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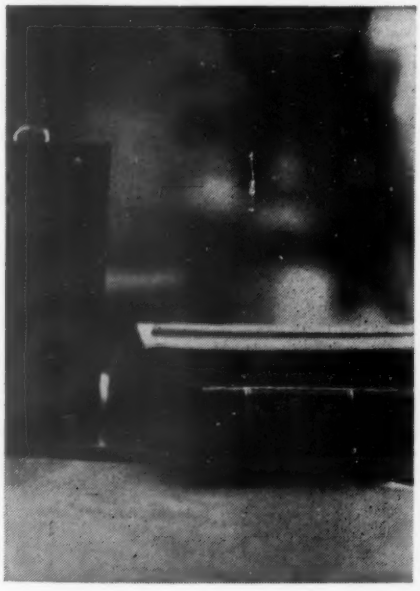

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American Journal of Hospital Pharmacy

American Society of Hospital Pharmacists

VOLUME 17 NUMBER 10 OCTOBER, 1960

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1. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958.
2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 15.

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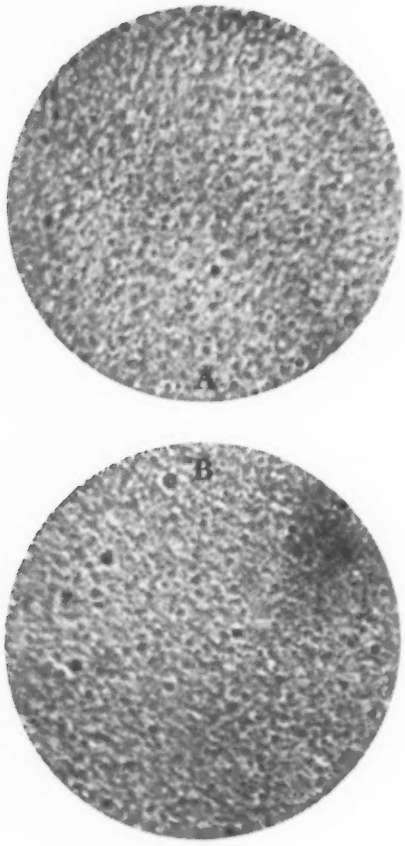

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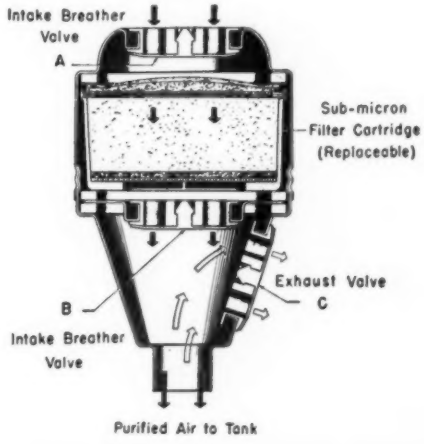

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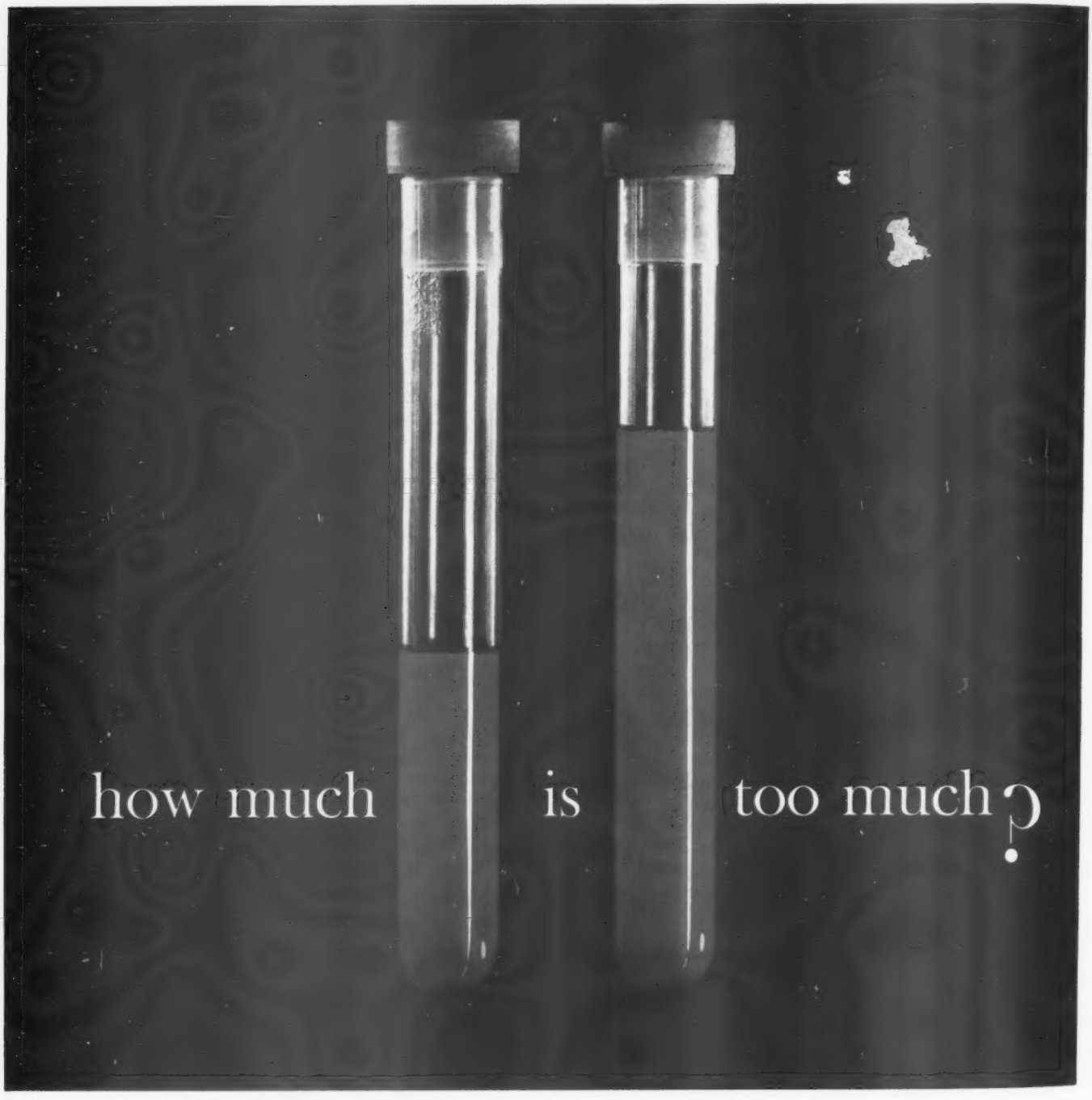

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1. Coblentz, A., and Bierman, H. R.: New England J. Med. 255:694, 1956. 2. McInnes, G. F.; Engler, H. S., and Saliba, N. R.: To be published. 3. Samuels, M. L.; Stehlin, J. S.; Dale, S. C., and Howe, C. D.: South. M. J. 52:207, 1959.

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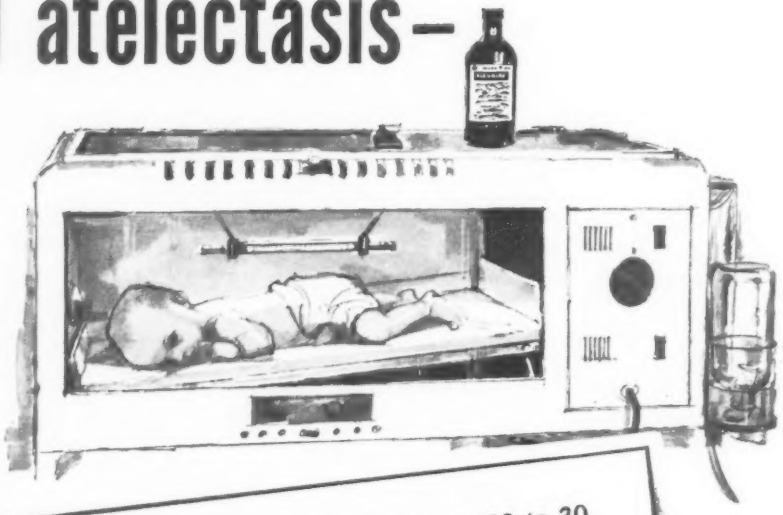
*". . . results are impressive. This dreaded condition usually improved in a few hours, and it was really striking to see a cyanotic baby with gasping respirations and suprasternal retraction become relaxed and pink in such a short period of time."**



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A typical Alevaire case history—D., a premature male infant (28 to 30 weeks) was delivered as a frank breech. Weight was 3 lb., 6 oz. After birth the patient's condition was poor; shallow, irregular respiration, suprasternal retraction, gasping and cyanosis were present. Breath sounds were diminished, and bilateral atelectatic rales were observed.

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*Smessaert, Andre; Collins, V. J.; and Kracum, V. D.: New York Jour. Med., 55:1587, June 1, 1955.

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Northern California Society

The 140th meeting of the Northern California Society of Hospital Pharmacists was held at the Upjohn plant in Menloe Park, on Tuesday, September 13.

President William E. Dudley called the meeting to order and then introduced Mr. Jack S. Heard, the immediate past Vice President of the ASHP. Mr. Heard reported on the important and controversial subjects which were discussed at the Annual Meeting of the ASHP and the Convention of the A.Ph.A. He also announced that Albany, New York and San Francisco, California will be the sites for the 1960 Institutes and the A.Ph.A. Convention is scheduled for Chicago, Illinois. The interest of the ASHP in the Good Ship S. S. HOPE, which is now being outfitted in San Francisco Bay, was also expressed by Mr. Heard. A delegation from this chapter visited the pharmacists on S. S. HOPE on September 15.

Ed Chilgren's Placement Report for August and a condensed report on the 23 resolutions offered at the A.Ph.A. Convention were read by Secretary George J. Gruber.

Mr. Dwight Moore, Upjohn Sales Manager and host for the evening, showed a film on "Current Trends in Treatment of Diabetes." The film was followed by a tour of the Upjohn plant and refreshments in the cafeteria.

Midwest Association of Sister Pharmacists

On September 15 the Midwest Association of Sister Pharmacists held its first meeting of the year at Mercyville Sanitarium, Aurora (Illinois) at the invitation of Sister M. Kateri. A member of the staff presented a discussion and demonstration of hypnosis. Following this a tour of the hospital, which boasts of a new nurses' home and auditorium, was made. A buffet luncheon was also served.

Indiana Chapter

The Indiana Chapter of the ASHP met at a luncheon meeting on Tuesday, June 21, in conjunction with the Indiana Pharmaceutical Association Convention in French Lick, Indiana.

A proposal was made to change the by-laws of the constitution to eliminate the necessity of meeting at French Lick. Since the Indiana Pharmaceutical Association's Convention will be in Indianapolis next year, a further study was recommended.

Dr. George F. Archambault, Pharmacist Director, Pharmacy Liaison Officer to the Office of the Surgeon General, Public Health Service, gave a very informative talk on "The Service of the Community Hospitals by Retail Pharmacists" at the afternoon session of the convention.

Greater St. Louis Association

The Hospital Pharmacists Association of Greater St. Louis held its annual installation dinner Friday night, September 9. The meeting was held at Carpenter's Hall, 1401 Hampton, St. Louis.

Mr. John Griffin of Cardinal Glennon Memorial Hospital was installed as President. Other officers installed were: *Vice-President*, Herman Coffman, Veterans Hospital; *Secretary*, Jack Jue, St. Mary's Hospital; and *Treasurer*, Emmett Skinner, Missouri Baptist Hospital.

Mr. Eugene Clark, President of the Board of Trustees of the St. Louis College of Pharmacy, gave the installation address. He spoke on the current problems in pharmacy and the proper handling of these problems as responsible pharmacists.

Mr. John Griffin, the new president, outlined the program to enlist the membership of every hospital pharmacist in the St. Louis Area. Its primary constituents are good public relations and interesting meetings to encourage attendance.

New Jersey Society

The New Jersey Society of Hospital Pharmacists held its first meeting of the new season at Presbyterian Hospital unit of the United Hospital of Newark, on the evening of Thursday, September 15. Vice-President Henry Roche presided in the absence of President Florence Sena Frick.

Members of the Society were welcomed by Mr. Donald M. Rosenberger, administrator of the Presbyterian Hospital, who also outlined for the group the history of the hospital and the later formation of the United Hospitals. Following supper, the pharmacists held their meeting. Reports of the Society's delegates to the Annual Meeting of the ASHP and the Convention of the A.Ph.A. were presented. The program for the season includes a Hospital Pharmacy Seminar to be held at Rutgers University in New Brunswick on Saturday

CONTINUED ON PAGE 18

Officers of the New Jersey Society were installed at a Spring meeting. Shown left to right are Victor Ern, Treasurer; Joyce Dolecki, Secretary; Dean Roy A. Bowers who served as installing officer; Henry Roche, Vice-President; Florence Frick, President and Eugene von Stanley, immediate past president

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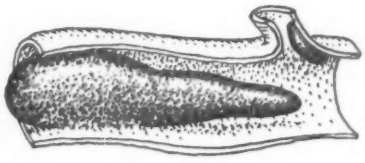
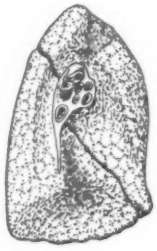
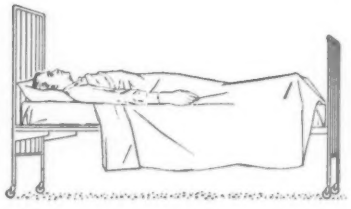
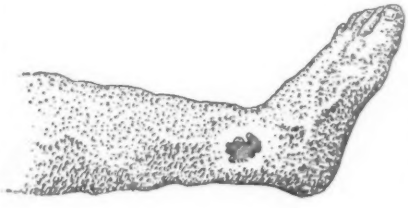
Results of therapy	Bed rest
Effect on intravascular thrombi	 Clot may form permanent obstruction to blood flow. New clots may form.
Effect on pulmonary emboli	 Sudden death from pulmonary embolism is an ever-present hazard. One or more nonfatal pulmonary emboli may result in irreversible lung damage or secondary pneumonia.
Effect on duration of illness and convalescence	 Weeks of hospitalization or bed rest at home are commonly required in the management of thrombophlebitis, phlebothrombosis, pulmonary embolism, and arterial thrombosis.
Frequency and severity of postphlebitic syndrome	 Chronic leg swelling, severe secondary varicose veins, and leg ulcers are common sequelae.

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CONTINUED FROM PAGE 15

evening, November 12. Plans were also completed for the Society's biennial dinner dance at the Hotel Robert Treat in Newark. In recognition of his 50 years of service as a pharmacist, arrangements were made for the presentation of a special award to Mr. Daniel Shea at the dinner dance. Mr. Shea is a pharmacist at the Nyak (New York) Hospital.

Following the meeting, there was a conducted tour of the pharmacy of Presbyterian Hospital, a moden, well planned, air conditioned unit. The space and equipment problems have been well taken care of in this pharmacy which could well serve as a model for others. Mr. William Dove, chief pharmacist and his assistants graciously explained various details and operations to their visitors.

Southeastern New York Chapter

The Southeastern New York State Chapter of the American Society of Hospital Pharmacists held a joint meeting with the Greater New York Chapter at St. Clares Hospital, Saturday, May 21. The meeting was preceded by a buffet luncheon which was arranged through the courtesy of the MacBick Company.

The meeting was presided over by Mr. Al Kessler in the absence of President Leo Blackman. It began at 2:15 with an opening prayer by Sister Bernadine. After introductory remarks, the program for the day was introduced.

Dr. K. Roth of Winthrop Laboratories spoke on "Tranquilizers and Muscle Relaxants." Her presentation took the form of a complete review of the tranquilizers available today according to their chemical grouping. In each group she discussed the indications, side effects, specific actions of the groups, etc. A data sheet was distributed which included about fifty commercial products, their generic names, groupings, and general comments.

A question and answer period followed, after which a report was given by Sister Donatus and Mr. Joel Yellin on the April meeting of the New York State Council of Hospital Pharmacists. The meeting was adjourned at 4:40, after which Sister Donatus hosted an informal gathering and tour through the Pharmacy.

The season's last meeting of the Southeastern New York State Chapter of the American Society of Hospital Pharmacists was held at The New York Hospital on Wednesday, June 22.

A letter from Mr. Leo Blackman in which he tendered his resignation as President was read by Mr. Kossler. Mr. Kossler thus became President, leaving the office of Vice-President vacant at this time.

Announcements included Mr. Al Deeb's appointment as Chairman of the Membership Committee. Mr. Bogash and Mr. Yellin were appointed as official Chapter delegates to the August meeting of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS and Mr. Gill Simon was appointed as an alternate.

The first speaker for the evening, Miss Winifred Sewall of the Squibb Medical Library, was then introduced. In her presentation she stressed proper organization of material, reference sources, the various methods used for cataloging and indexing material and the mechanics involved.

Following this, Mr. Harold Neham, discussed the hospital pharmacist's problem of the filing of drug information and developing a working professional library.

After an interesting question and answer period with Miss Sewall and Mr. Neham, a collation, courtesy of E. R. Squibb was served.

Secretaries of ASHP Affiliated Chapters are urged to send reports of meetings to the national secretary promptly. Since the AMERICAN JOURNAL OF HOSPITAL PHARMACY appears on a monthly basis, reports must be received within five days after the meeting in order to be included in the forthcoming issue. We urge you to send details of the activities of your chapter for publication in this column.

Western New York Chapter

On June 2 the Western New York Chapter met at the Veterans Administration Hospital in Buffalo. Results of the election for officers for the coming year were announced as follows: *President,* Kathleen DeClare, Niagara Falls Memorial Hospital, Niagara Falls; *Vice-President,* Francis X. Sturner, Buffalo General Hospital, Buffalo; *Recording Secretary,* Marlene Keata, Kenmore Mercy Hospital, Kenmore; *Corresponding Secretary,* Charles Hoff, Mercy Hospital, Buffalo; and *Treasurer,* Sister Mary Vera, Mercy Hospital, Buffalo.

As was decided last year, the immediate past president will represent the Chapter as the delegate to the Annual Meeting of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. In this case the delegate will be Mr. Melvin Monteith who will represent the Chapter at the Washington meetings.

Cleveland Society

On May 25, the Cleveland Society of Hospital Pharmacists held its Annual Banquet and election of officers at the Chef Louis Restaurant in Cleveland. Announcement of officers for the 1960-1961 term included *President,* Walter Markunas, Crile V. A. Hospital, Cleveland; *Vice-President,* Margaret Trevis, St. Luke's Hospital, Cleveland; *Secretary,* Mary Ann Yanosek, Euclid-Glenville Hospital, Cleveland; and *Treasurer,* Theresa R. Cook, Mt. Sinai Hospital, Cleveland.

Akron Area Society

The Akron Area Society of Hospital Pharmacists held its first meeting of the year on September 13 at Akron City Hospital, Committee chairmen were appointed as follows: *Program,* Ed Bolchazi; *Public Relations,* Wayne Eaton; *Student Project,* Mary Morgan; *Membership,* Jeanne Sickafoose; *Nominations,* Corrine Rho; *Emergency and Disaster Program,* Charles King, Jr.; *High School Project and Scholarship Program,* Mary Morgan; *Constitution and By-Laws,* Jeanne Sickafoose; and *Banquet,* Ed Bolchazi.

Highlights of the A.Ph.A. Convention and the ASHP Annual Meeting were presented by Mrs. Sickafoose. Comments were also given on the summer Institutes by Mr. John McGowan and Mr. Ed Bolchazi.

Plans for future meetings were discussed. Of particular interest was Career Day which was held by St. Thomas School in Akron on October 18 and 19. Several members volunteered their time for work in the Pharmacy Booth.

Oregon Society

The following officers were elected in September to serve for the coming year: *President,* Richard Neal, Portland; *Vice-President,* Roy Ward, Good Samaritan Hospital, Corvallis; and *Secretary-Treasurer,* Eleanor Davidson, Portland.

Houston Area Society

A regular meeting of the Houston Area Society of Hospital Pharmacists was held July 10 at 3 P.M. at John Sealy Hospital in Galveston, Texas. A tour of the pharmacy was first made by all present. An interesting feature of the tour was the tablet-counting machine, an import from Germany, which was demonstrated by Miss Beaulieu, a University of Texas Pharmacy student, and the daughter of Florence Beaulieu of the John Sealy Hospital staff.

The business meeting took place in the cafeteria and was presided over by Jack Farmer, *Vice-President,* in the absence of Mr. McIntosh.

An excellent report was given by Ben Parma on the Institute he attended in Columbus, Ohio, in June. This was followed by the demonstration of some new equipment.

Four new members joining the Houston Area Society include Florence Wittig, Joseph Clift, and Eustacio Galvan, all of the John Sealy Hospital staff, Galveston; and Robert McWhorter from Beaumont.

A buffet sponsored by Baxter Laboratories was followed by a movie produced by Winthrop Laboratories on the problems of resistant staphlococcic infections.

Virginia Society

Officers for the coming year were recently elected by the Virginia Society of Hospital Pharmacists. The new President is Andrew W. Abbitt of 121 Berkeley Lane, Williamsburg. Other officers are *Vice-President,* Lloyd Dixon, Kecoughton V.A. Hospital, Hampton, and *Secretary-Treasurer,* Justine Wilkins, Medical College of Pharmacy, 1200 East Broad Street, Richmond.

Wisconsin Society

The Wisconsin Society of Hospital Pharmacists held its first meeting on September 23 at St. Catherine Hospital in Kenosha. Mr. Ernest P. Celebre was host for the evening. The meeting included a panel discussion on pricing.

New officers for the coming year are: *President,* Sister Mary Natalie, Milwaukee; *Vice-President,* George A. Wright, Milwaukee; and *Secretary-Treasurer,* Virginia McVey, also of Milwaukee.

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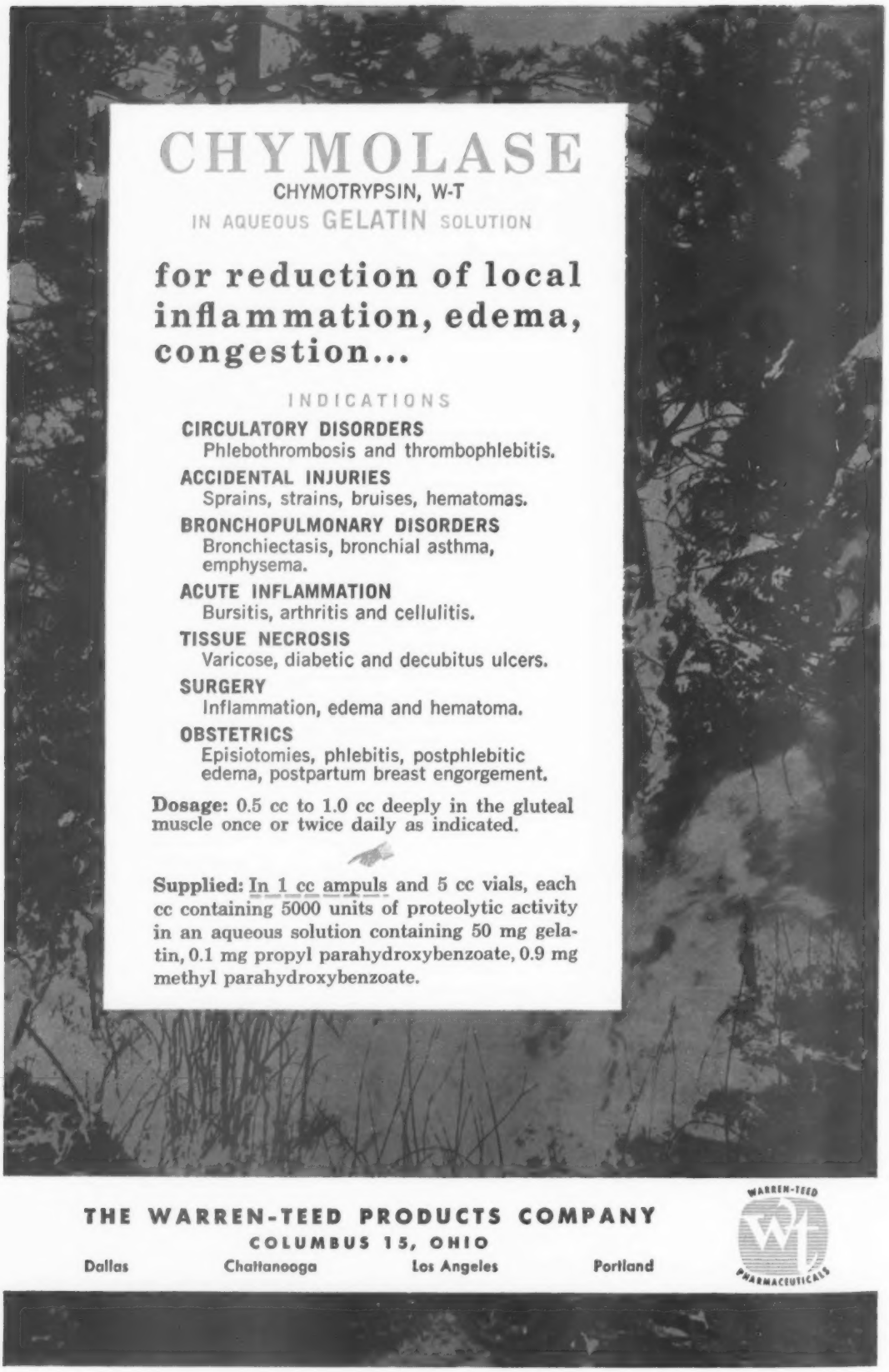

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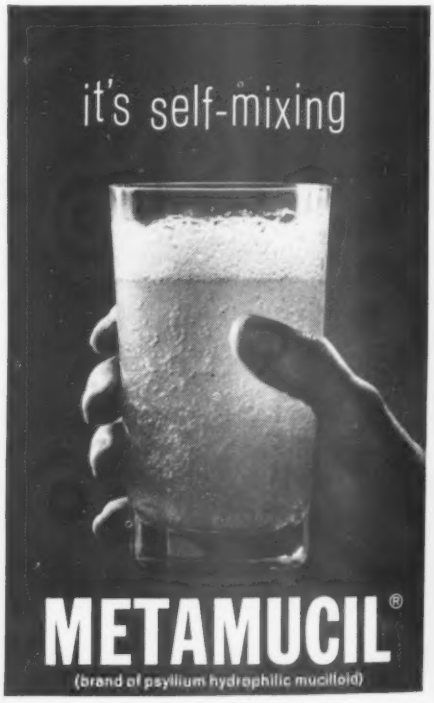

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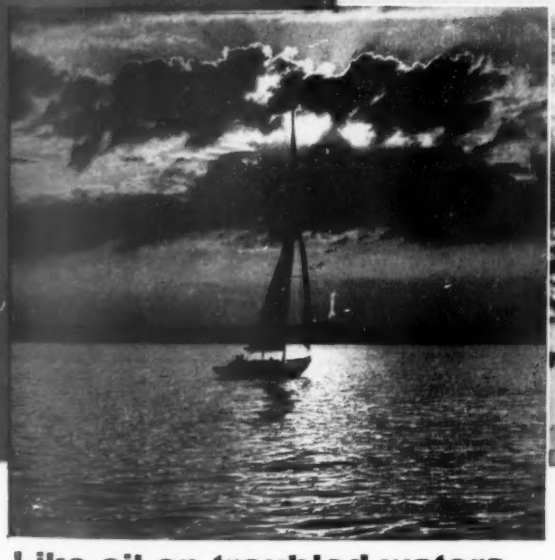

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newsletter

EIGHTH OF A SERIES WITH SIGNIFICANT SUGGESTIONS FOR CONTROLLING CROSS INFECTION

MORE and more each month as everyone—those in the hospital as well as others of us concerned with infection control—learns more about the continuing importance of the problem, we seem to be getting an increasing number of requests for specific instructions on not only "how to" but "how frequently" disinfectants should be applied. Fortunately, the simplicity of applying Amphyl®, O-syl®, or Lysol® disinfectants, and Tergisyl® detergent-disinfectant, makes it possible for us to furnish you with easy-to-follow instructions on any one of them. The frequency with which they need to be used in various applications, however, may vary widely depending upon the degree of environmental contamination to which the particular area is exposed. Many hospitals have done their own bacteriological testing and set up their own standards of frequency on various services. For general guidance, you may find the following suggestions helpful.

Writing on "Sanitation in Patient Care Areas", Dr. Ruth B. Kundsin (Journal of the American Medical Women's Association, January, 1960) emphasizes the dangers of bacterial fall-out from commonplace hospital activities and suggests two methods of attack: 1) to decrease fall-out by a careful re-evaluation of activities, and 2) to destroy bacteria deposited. Among the recommendations made to accomplish the latter is disinfection of floors by the wet pickup technic on the following schedule: "daily disinfection—corridors, delivery room, dressing room, emergency ward, isolation rooms, nursery, pediatric ward, and utility rooms; weekly disinfection—medical ward and surgical ward; and terminal disinfection—autopsy room, single room, maternity ward, and operating room."

Dr. H. Taylor Caswell and his co-workers at the 900-bed Temple University Medical Center reveal some interesting figures on both the incidence and control of staphylococcal infections as experienced over three years with 60,000 admissions a year. (Surgery, Gynecology & Obstetrics, May, 1960) While infection in 10,000 clean surgical wounds each year decreased approximately 60%, there was an appreciable increase in hospital related medical infections with phage type 80/81 identified in 71%. Concurrently, the number of patients admitted for treatment of staphylococcal disease doubled—emphasizing the hospital's problem in care of this constant flow of heavily contaminated patients into the hospital from the community.

May we again mention that one of the best dramatizations of how the staph-infected patient can contaminate the hospital is shown in the color motion picture, "Hospital Sepsis: A Communicable Disease", sponsored jointly by the AHA, AMA, and ACS on an industry grant with technical supervision by Dr. Carl W. Walter? When this film is shown in your hospital, be sure to see it. An essential measure recommended to control spread of staph through the environment is generous use of bactericidal cleaning methods.

L & F's Tergisyl® detergent-disinfectant fits the recommendations made by Dr. Walter when describing his floor-flooding technic at a Massachusetts Medical Society meeting—that a synthetic phenolic is the product of choice for operating room floor care. We have just revised our 24-page booklet on Tergisyl and would be glad to send you a copy, or as many copies as you would like for teaching purposes. Included are suggestions for use of this combined cleaning and disinfecting agent in all areas of the hospital in the economical new 1:100 dilution. Tergisyl is also the detergent-disinfectant used at Huggins Hospital in Wolfeboro, New Hampshire, under Dr. Ralph Adams' instructions, to achieve "near sterility" of operating room floors, walls, and furniture following his "zone concept" of bacteriologic cleanliness. (SG&O, March, 1960) If you would like this new booklet, a reprint of Dr. Adams' article, and Tergisyl samples, please write us.

Are you concerned about adequate chemical disinfection of catheters? So much has been in the literature recently on the dangers of inadequate sterilization that we wouldn't be surprised if you were. To help you meet this problem, we have prepared an instruction card on O-syl® disinfectant specifically on this subject. The card is designed so that it may be posted for permanent instructions, or we will send you multiple copies for teaching purposes if you wish. Just let us know which you want. O-syl's broad microbicidal activity against a wide variety of enteric organisms as well as Staphylococci, Pseudomonas, and TB bacilli recommends it for this use.

Focusing their attention on gram-negative bacilli, Dr. Hans H. Zinsser and his co-workers from the Department of Urology at Columbia University College of Physicians and Surgeons report alarmingly high mortality from septicemias due to urinary infections as follows: E. coli bacteremias, 38%; Aerobacter aerogenes, 60%; and Pseudomonas aeruginosa, 75%. While they were successful in reducing mortality from Aerobacter aerogenes septicemia in 1958 and 1959 60%, the incidence increased 300%, pointing up the great need for combatting the changing bacterial flora in the hospital with aseptic cleanliness. (The Journal of Urology, page 755, May, 1960)

Some of you will be reading this letter before the American Hospital Association meeting in San Francisco and some afterwards. Others may be seeing it before the American Public Health Association meeting, which is also in San Francisco this Fall. If you are at either of these meetings, we hope you will stop and visit us at our exhibit booth.

Charles F. Manz
General Sales Manager
Professional Division

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Dear Sirs:

Certification Laboratory

DEAR SIRS: I do not usually resort to writing comments to Editors but I was riled slightly by the item which Mrs. Evlyn Gray Scott quoted from *Drug and Cosmetic Industry* in her letter appearing in the August issue of the AMERICAN JOURNAL OF HOSPITAL PHARMACY.

To quote a portion of a paragraph ". . . No one can expect the retail pharmacist to check the quality of all the medicinals he buys for compounding purposes. He lacks the training, the time, and the money to pursue such a practice. . ." The thing I object to is the idea that some foreign professions have, foreign to pharmacy that is, suggested that a pharmacist lacks the *training* to pursue such a practice. This idea is not only current among non-pharmacists as it seems to be among some so-called pharmacists themselves. The training I received when in school permitted me to pursue much along this line, and I believe that most pharmacists today receive this training. If they do not, then the five years they are spending in pharmacy training today is surely wasted. The average pharmacist graduating from our schools these days is very capable of doing this testing and assaying. He may not have the time or money to do so, but he surely is capable. Pharmacists today seem to be satisfied to pursue a life of super-salesmanship in retail pharmacy or a sedate life of acting as a pharmaceutical warehouseman for a hospital rather than practice the profession they have been prepared for. There is a great deal more in store for these people if they would only use what they spend years to acquire. There are many dedicated pharmacists such as are found within the ASHP who have dedicated themselves to the furtherance of pharmacy and who can and do use the many facets of pharmacy which they have been taught to good avail. I am sure there are many in retail pharmacy such as those engaged in the so-called professional pharmacy that are likewise able. But, I do resent having anyone tell me that a pharmacist lacks the *training* to do these things. This is not true and if a pharmacist finds it is, then his schooling surely cheated him out of something to which he is entitled.

I hope that there are not many pharmacists who feel that they are not capable of checking the quality of the items he uses for compounding because he is lacking in training.

R. H. KLOTZMAN, Ph.G. B.S.

2816 Sixth Avenue
Great Falls, Montana

Narcotic Reprint

DEAR SIRS: I thought that your letter to the administrators of hospitals in our country, along with the reprint from THE BULLETIN on "Regulations for Handling of Narcotics" was well done and certainly a step that should help cement the relationships between some of our administrators and the status of hospital pharmacists.

EDWARD SUPERSTINE, *Chief Pharmacist*

Metropolitan Hospital
1800 Tuxedo Avenue
Detroit 6, Michigan

DEAR SIRS: I would like to obtain twelve copies of the reprint, "Regulations for Handling Narcotics." We plan to use these in in-service education, and on our nursing stations. Thank you . . .

BEATRICE R. SHERRILL, R. N.

Methodist Hospital
Hattiesburg, Mississippi

From an Honorary Member

DEAR SIRS: . . . It was a very pleasant and unexpected surprise when I received your message informing me of my election to Honorary Membership in the SOCIETY. This is one of the finest things that has every happened to me. Will you express my sincere thanks and appreciation to the officers and membership for the honor they have bestowed on me.

HANS S. HANSEN

St. Agnes Hospital
Fresno 5, California

EDITOR'S NOTE: Mr. Hans S. Hansen, president of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS for the 1946-1947 term, was elected an Honorary Member of the SOCIETY at the 1960 Annual Meeting.

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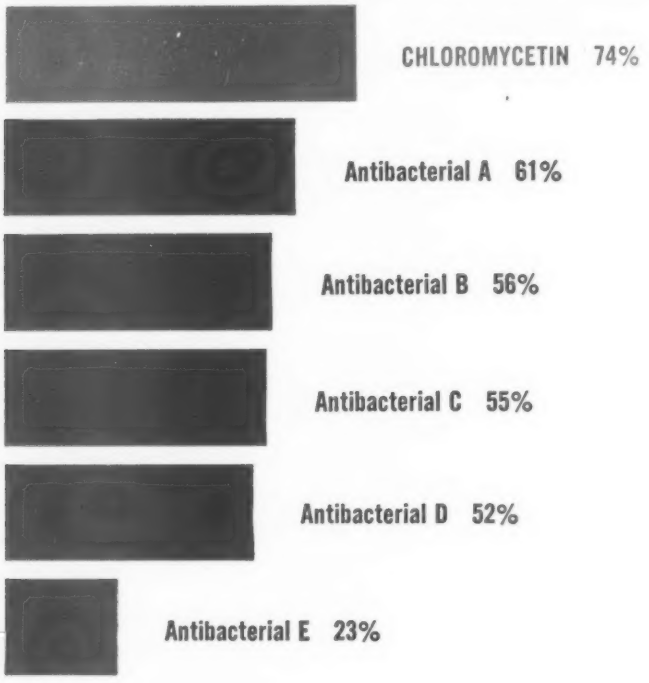

*Adapted from Goodier, T. E. W., & Parry, W. R.: *Lancet* 1:356, 1959.

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by DON E. FRANCKE

Guiding Principles Of Formulary System

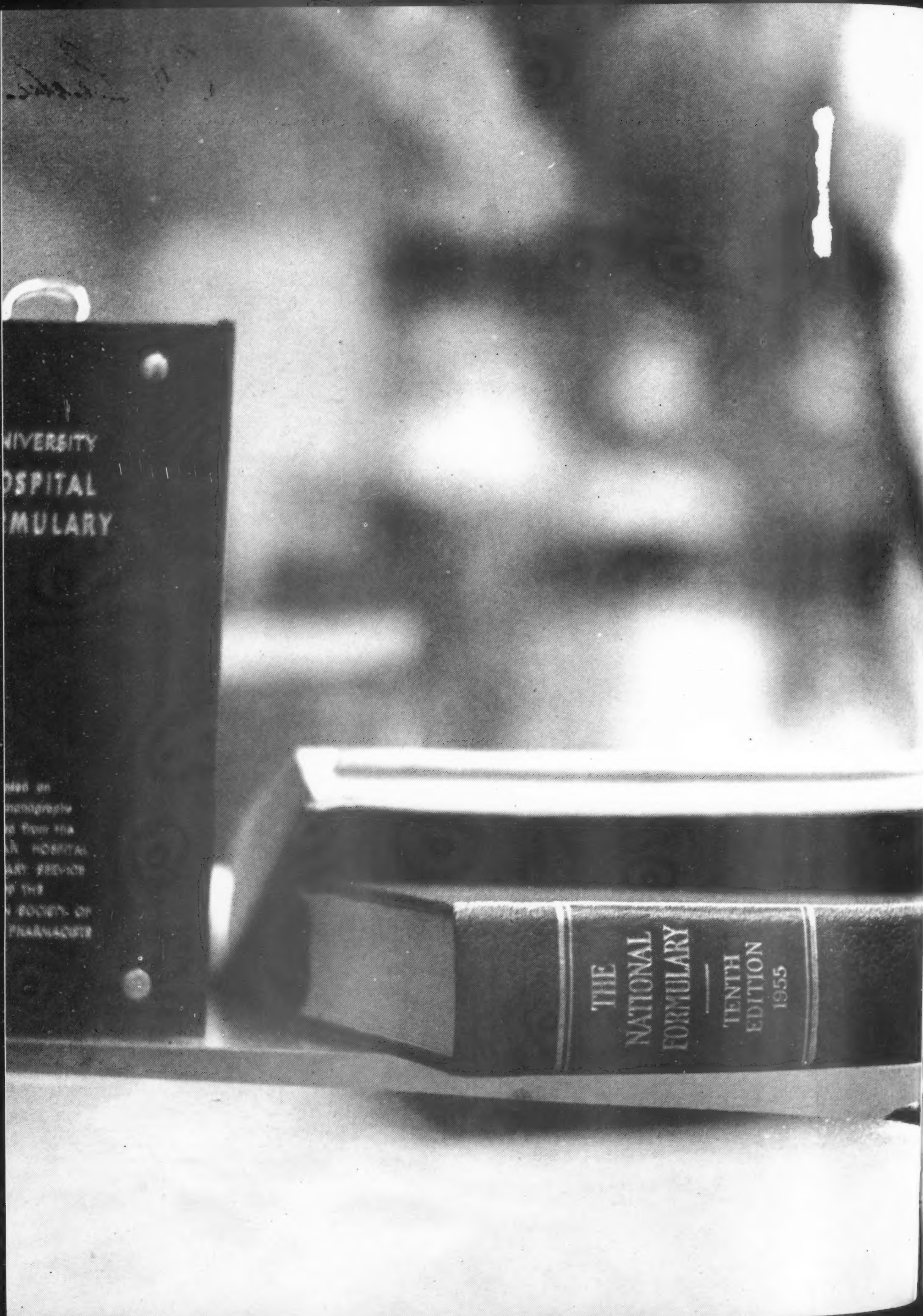
► THE FORMULARY SYSTEM AND HOSPITAL formularies have existed in this country since the days of the American Revolution when the *Lititz Pharmacopoeia* was published in 1778 for use by the Continental forces. It was not until 1816, however, that a formulary for a private civilian hospital was compiled and it is noteworthy that the *Pharmacopoeia of the New York Hospital* was published "under the authority of the physicians of that institution." In fact, much later, it was Dr. W. J. Stainsby, a physician at New York Hospital, who, with the pharmacologist Dr. Robert A. Hatcher, formulated the first guiding principles for the operation of the formulary system. The recommendations of Stainsby and Hatcher were published in both the *Journal of the American Medical Association* [101:1802 (Dec. 2) 1933] and the *Journal of the American Pharmaceutical Association* [22:1281 (Dec.) 1933], and greatly influenced the development of formularies in American hospitals. The principles set forth by these men have guided the operation of the formulary system in hospitals during recent years.

In 1936 a new concept was introduced into the operation of the formulary system—one which recognized the importance of establishing formal liaison between the hospital pharmacist and the medical staff. This came with the adoption of the first Minimum Standard for Pharmacies in Hospitals by the American College of Surgeons. This document was the work of Dean Edward Spease, who at that time was directing the School of Pharmacy at Western Reserve University, and Robert Porter, who was the Chief Pharmacist at Western Reserve University Hospitals in Cleveland. Spease and Porter sagaciously recognized that there existed nowhere in the hospital a medium through which the chief pharmacist could formally communicate with the medical staff. True, the chief pharmacist was a department head; true, he could discuss problems at medical staff meetings and resolve questions with individual physicians. But there was no organized group within the hospital which contained representatives of both medicine and pharmacy and which assigned to the pharmacist specific responsibilities and privileges. Spease and Porter filled this need by recommending the establishment of a Pharmacy Committee with the pharmacist as permanent secretary. This recommendation was, of course, adopted by the American College of Surgeons and has been carried forward and strengthened in the revised Minimum Standard of which the section devoted to the Pharmacy and Therapeutics Committee forms an integral part.

During recent years there has been an increased need, however, to spell out more completely the purposes, organization, functions and scope of the Pharmacy and Therapeutics Committee and to establish and implement more detailed and clear-cut principles for the operation of the formulary system. This need has arisen partly due to the greatly increased volume of drugs dispensed in hospitals, partly because of the large increase in the number of drugs and their combinations available, and partly due to certain marketing practices of the pharmaceutical industry. To meet this need, the Joint Committee of the American Hospital Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS has drafted a "Statement on the Pharmacy and Therapeutics Committee" (page 611), a "Statement on the Guiding Principles on the Operation of the Hospital Formulary System" (page 609), and a "Statement of Principles Involved in the Use of Investigational Drugs in Hospitals" (page 612). Each of these statements, which concern the handling of drugs in hospitals, has been approved by the executive bodies of the respective organizations.

But guiding principles must be analyzed and interpreted in the light of everyday practices if they are to find widespread adoption. Of immense help in this respect is the discussion by Alanson W. Willcox of "The Legal Basis of the Formulary System" (page 602). As Mr. Willcox emphasizes, "A major difficulty in the past has been that hospital practices have varied in particulars bearing upon legality, with the result that arguments pro and con have often failed to meet because they were based on different assumptions regarding the manner of operation." Mr. Willcox has prepared a lucid discussion of the subject clearly setting forth the importance of basic principles and emphasizing the fundamental role of the medical staff in the operation of the formulary system.

The formulary system is sound in principle. It is an effective method for the evaluation and selection of drugs in hospitals. Its successful operation must always rest upon the informed cooperation of the medical staff. But, in the operation of the formulary system, the hospital pharmacist plays an essential role as secretary of the Pharmacy and Therapeutics Committee and as the responsible head of the pharmacy department. Upon him rests, to a major extent, the responsibility of a valid hospital formulary program. The statements and discussion published in this issue of the JOURNAL should aid him in carrying out this important professional responsibility.


THE NATIONAL FORMULARY
TENTH EDITION 1955

THE LEGAL BASIS OF THE FORMULARY SYSTEM

by ALANSON W. WILLCOX

► THE LEGALITY OF THE FORMULARY SYSTEM OF dispensing drugs in hospitals can be discussed more intelligently in light of the guiding principles approved by the American Hospital Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. A major difficulty in the past has been that hospital practices have varied in particulars bearing upon legality, with the result that arguments pro and con have often failed to meet because they were based on different assumptions regarding the manner of operation. Since the assumptions have often been unexpressed, confusion has been considerable.

The purpose of the present paper is to explain the need for the legal precautions recommended by the guiding principles, and to indicate how they will serve to protect the legality of the formulary system as it generally operates.

The accompanying opinion of Boynton Livingston, Esq., concludes that these precautions avoid infringement of trademark right. In the opinion of the present author, the same precautions also avoid violation of the Federal Food, Drug, and Cosmetic Act, and they should avoid conflict with state laws in most if not all of the states. The wording of state laws varies, however, and it is possible that in a few states the guiding principles may require modification in some particulars. Local court decisions and attorney general opinions must be examined, to make certain that none stands in the way. For all these reasons, only an attorney practicing in the state can take responsibility for the legality of the formulary system in that state.

ALANSON W. WILLCOX, a graduate of the Harvard Law School, is General Counsel of the American Hospital Association.

Presented at the annual meeting of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, Washington, D. C. 17 August 1960.

This article is being published simultaneously in *Hospitals*, The Journal of The American Hospital Association.

Necessity of Agreement by Physician

There would be no "formulary problem" for the lawyers if in all prescriptions[1] the drugs ordered were described by their official or nonproprietary names. The only problem inherent in the system arises because, when prescriptions are written by proprietary names, the system stipulates that in normal course the prescriptions will be filled without reference to brand identity. But for the agreement of the prescribers authorizing this course, it would be an illegal procedure, and the guiding principles point out that it should not be fol-

lowed in any instance in which the prescriber indicates in an appropriate manner that he does not wish it followed.

A prescription affords the pharmacy or hospital its only legal authority to dispense or administer a drug bearing the prescription legend. This means that the dispensing or administering is illegal if it is not in accordance with the physician's authorization or consent, even though the disparity consists only in a variance between products chemically and therapeutically identical but of different brands.[2] If the drug has moved in interstate commerce, dispensing of a brand not authorized or consented to by the physician may be a technical violation of the Federal Food, Drug, and Cosmetic Act; and more important, it is in most states a violation of state anti-substitution laws or regulations.

There are ample reasons, legal as well as non-legal, to guard against unauthorized dispensing or administering of drugs. Even where no health hazard is involved, as in the case of drugs chemically and therapeutically identical, there may be a material risk of disciplinary proceedings against the pharmacist, which could lead to suspension or revocation of his license. The hospital board of trustees or medical staff or administrator cannot justifiably expose the pharmacist to this risk. There is also the ever-present possibility of criminal prosecution of the pharmacist and perhaps of others—doubtless a slight risk as long as all goes well, but a risk not to be courted needlessly. Finally, although the chance of injuring a patient by dispensing one brand rather than another is extremely slight, medication errors do occur from time to time, and the defense of a case based on medication error would be more difficult if it could be shown that the physician's order had been disregarded without his consent.

For all these reasons, dispensing not authorized or consented to must be avoided. The question is how this can be done consistently with use of a hospital formulary.

The simplest method, from the lawyer's point of view, would be to require all physicians to write all prescriptions by the official or nonproprietary names of the drugs prescribed. If such a requirement could be made and enforced, there would be no legal problem in filling the prescriptions or labeling the containers. Unfortunately, however, such a blanket requirement is generally thought impractical of application to the entire medical staff. If any hospital were prepared to apply such a requirement to its house officers, and apply it rigorously, the consent of these officers called for by the guiding principles could be dispensed with.

Imprint on Prescription Forms

Precisely the same legal effect as the writing of a prescription by nonproprietary name can be obtained by an imprint on prescription forms, suggested by the guiding principles as an optional procedure. Thus, if a physician signs a prescription in a proprietary name, but bearing the statement "dispensing by nonproprietary name authorized unless checked here ☐" or similar wording, the meaning is clear. Unless the physician "checks here" he has written a prescription in the alternative, calling for either the brand which he has named or any other brand of the same basic drug. Whichever way the pharmacist fills it, he is acting in strict and literal accord with the prescription.

Here again, however, what is an obvious and simple procedure from the lawyer's point of view encounters difficulties in practical operation. It is awkward to place the necessary imprint on all the many hospital forms and in all the places where medication orders may appear; physicians occasionally use prescription blanks they have brought from their offices; in emergencies drug orders may be given orally and confirmed later. The imprint device, in short, although a useful supplementary mechanism, is not for most hospitals a satisfactory overall means of authorizing application of the formulary system.

It is for these reasons that a general authorization given in advance, by all staff physicians and all other prescribers who may use proprietary names, is generally a prerequisite to the operation of a hospital formulary system. Let us consider, first, whether physicians are permitted by law to give such general authorization; second, the manner in which the authorization should be manifested; and third, its legal effect as protection to the pharmacist.

1. The word "prescription" as used throughout this paper includes what in hospital parlance is described as a "medication order." It may consist merely of a notation on the patient's chart.

2. It is no defense that limitations imposed by the physician may be unimportant, or even ill-advised.

Legality of General Consent

The legality of general consent, as prior authorization has usually been called,[3] has been questioned on the ground that it constitutes an unlawful surrender of professional judgment, which medical practice acts require to remain untrammeled. So far as this author is aware, such an argument has never been directed against a formulary system which, like that envisaged by the guiding principles, provides a ready means by which the physician may insist upon a particular brand of drug in any instance in which he deems such action wise. The argument, nevertheless, should be examined on its merits.

When a physician accepts the privilege of practicing in a hospital he commonly yields to the medical staff as a whole, so far as his practice in that hospital is concerned, certain professional decisions which he is otherwise free to make for himself. If he disapproves of the operating room procedures, or the limitation on the use of oxygen for premature infants, or a requirement of consultation in certain circumstances, or the surveillance of his work by the tissue committee—to pick examples at random—he is free to take his patients elsewhere and practice as his own judgment may dictate. But he is not free to disregard, in that hospital, the reasonable rules established pursuant to the consensus of his professional peers. So the courts have held. Generally speaking, the better the hospital and the better its medical staff, the greater the controls over the individual physician; indeed, these controls have become the hallmark of good medical practice in hospitals, and a prerequisite to hospital accreditation.

The hospital formulary system, as stated in the guiding principles, "is the accepted method whereby the medical staff of a hospital, working through a Pharmacy and Therapeutics Committee selected by it, evaluates, appraises and selects from among the numerous medicinal agents available, those that are considered most useful in patient care, together with the pharmaceutical preparations in which they may be administered most effectively." In view of the number and variety of pharmaceuticals that are available today, and the rate at which new ones are being developed, it is evident that the typical practicing physician cannot appraise their relative value as effectively as can a group especially charged with this responsibility. As in other aspects of hospital practice (but to a lesser extent because of his reserved right to make exceptions), the physician subordinates his judgment to an informed opinion arrived at by a staff committee and concurred in by the medical staff as a whole. Seen in this light, the restriction implicit in the formulary system is a lesser invasion of the physician's professional prerogatives than are many other provisions of the bylaws of a hospital medical staff.

If the primary purpose of the formulary system to improve patient care were not intermingled with and sometimes obscured by economic considerations, probably the propriety of its acceptance by physicians would never have been questioned. But the fact that the system may save money as well as promote a high quality of care is hardly a valid argument against it. It cannot be assumed that the medical staff will subordinate health to economy in respect to the purchase of drugs, any more than it will do so in other aspects of medical care.

At any rate, the system recommended in the guiding principles preserves the physician's full freedom of action, by permitting him to stipulate a particular brand of drug in any case in which he finds reason to do so. With this right reserved, the legality of his participation in the system seems not open to question.

Evidencing General Consent

The advantage of having the authorization by staff physicians and other prescribers expressed in writing is self-evident.

A physician who accepts and exercises staff privileges in a hospital, knowing that the formulary system is in effect, would probably be found by a court to have agreed to it; but argument and uncertainty, and the risk of faulty memory or faulty understanding by individuals concerned, can be avoided by a very simple writing. In case a hospital or its pharmacist is challenged by a state board of pharmacy, either of them is in a far more comfortable position if a written authorization by all staff physicians and other prescribers is on hand.

If the formulary procedures are set forth in the medical staff bylaws, or the medical staff rules, a written agreement in general terms to abide by the bylaws and rules would seem to be sufficient. Insertion of a reference in the subscription clause, however, specifically authorizing application of the formulary system to the signer's prescriptions where he does not otherwise indicate, makes clear beyond dispute that he is knowingly and intentionally accepting the formulary procedures.

Some lawyers believe that a separate document, which may be the only method for house officers who customarily do not sign the bylaws, is a preferable method of obtaining authorization by members of the medical staff as well. A separate document, like a special reference in the subscription to the bylaws, makes clear that attention has been focused on the formulary system. Such a document should refer to a written statement of the formulary policies and procedures (whether the statement appears in the bylaws or else-

3. The words "authorization" and "consent" are for present purposes interchangeable, but "authorization" seems more descriptive in that it suggests the affirmative role of the physicians in the formulary system, as distinguished from the passive acquiescence which might be suggested by the word "consent."

where) and recite that the signer is familiar with that statement.

The existence of the necessary authorization or consent is a matter of fact, and there is no rule of law about the manner of its proof. But it is a matter of such importance to both the hospital and the pharmacist that in self-protection they ought to put their ability to prove it beyond the realm of argument. Signatures on an appropriate document are by all odds the best way to do this. In protection to itself and in fairness to its pharmacist, a hospital ought not to apply its formulary system to the prescriptions of any physician unless it has on file a signed and unrevoked authorization by that physician.

Effect of General Consent

It has been emphasized above that a pharmacist is protected in dispensing a prescription drug only if he acts in accord with the direction of a physician. How, then, does the existence of a general authorization or consent alter the situation when an individual prescription written by proprietary name, without further indication of the physician's intent, is presented to the pharmacist?

The first question is what a prescription means when it is written in this form by a physician who has agreed to the formulary system.

Even if we look at the actual or subjective intention of the physician, the probability is very strong indeed that he intended to call merely for the basic drug in question, and that he used the proprietary name only as a more convenient means of reference to the basic drug. If that was not his actual intention he was careless, for he knew or should have known that the pharmacist would so interpret the prescription, and that insistence upon a particular brand required some indication beyond the mere use of the proprietary name.

To a lawyer, however, the question is not what actual intention the physician may have harbored when he wrote the prescription, but what intention he has manifested to the pharmacist by the writing. What would "the ordinary prudent man" in the pharmacist's position, knowing what the pharmacist knows, believe to be the physician's intent?[4]

When a physician in a hospital following the formulary system gives a written or oral prescription by proprietary name, without further indication of his intent, he knows, and knows that the pharmacist knows, (1) that the physician has signed a general authorization to fill prescriptions by nonproprietary name, (2) that he has not revoked this authorization, as he has a legal right to do at any time, (3) that in the absence of contrary indication by the physician, the prescription will be filled in accordance with the rules of the formulary, and (4) that he has given no contrary indication. Under these circumstances, the fair and reasonable meaning to the pharmacist is that he is authorized to dispense the basic drug ordered, in accordance with the formulary system and without regard to brand identity.

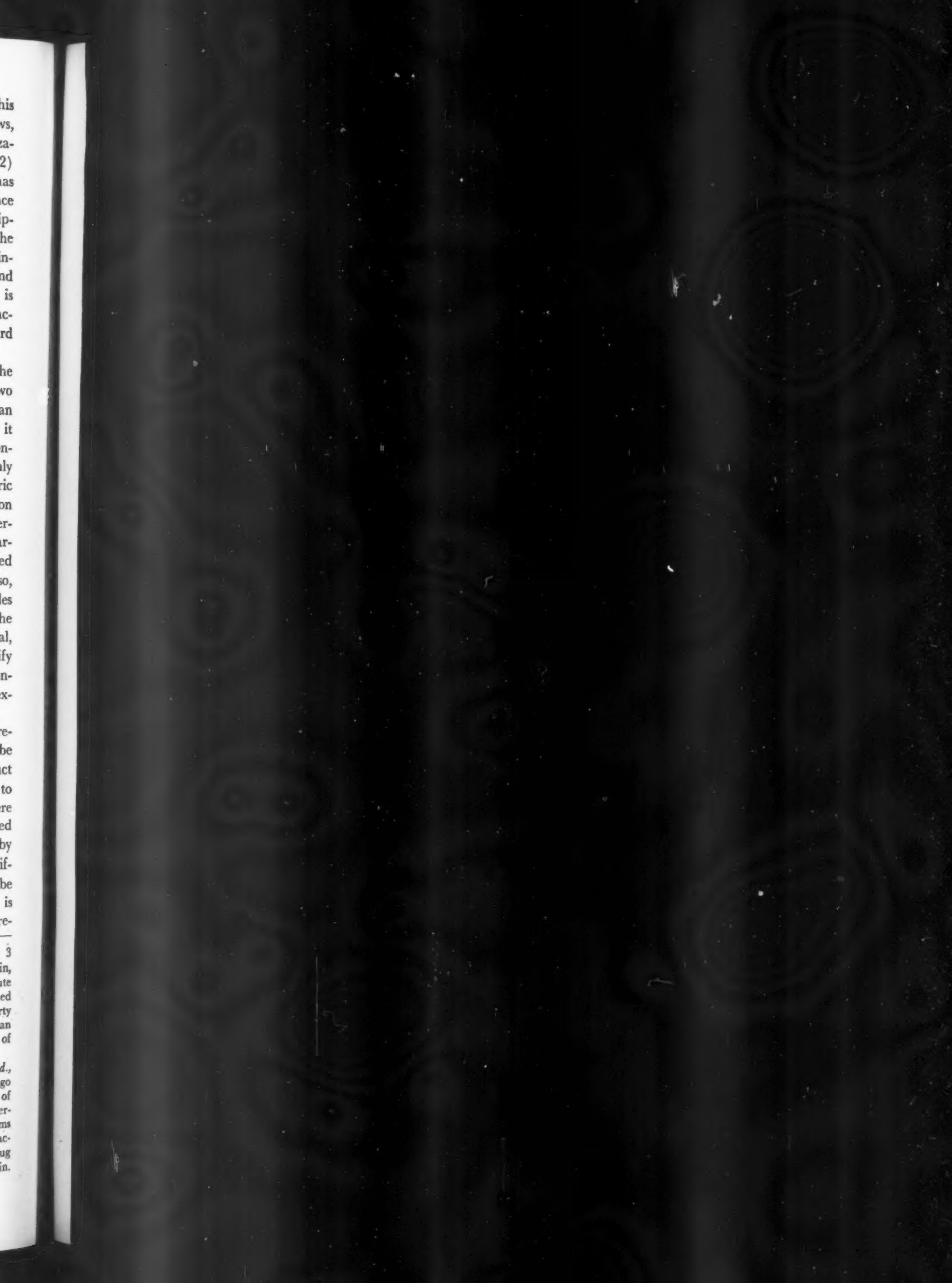
A prescription is not intended to be read by the general public. It is a communication between two individuals, the physician and the pharmacist, and can only be read in the light of their knowledge. Whether it is written by trade or nonproprietary name, it conveys to the recipient the meaning of the sender only because they share an understanding of the esoteric symbols used. No court could interpret a prescription without the aid of expert testimony—without considering what it means, not to a layman, but to the pharmacist recipient. What it means to him is governed partly by pharmaceutical terminology, but partly also, if he is operating under a formulary system, by the rules of the formulary system. In a lawyer's language, the formulary system is a "local usage" within the hospital, and all authorities agree that a local usage may modify the meaning of a writing.[5] Here, the modification consists in reading into the prescription a term not expressed, "or the formulary equivalent."

Even if a court were reluctant to interpret the prescription in this fashion, however, the result would be the same because the order for a proprietary product would in effect be accompanied by an authorization to dispense any other brand of the same basic drug. There can be no question that if two documents were handed to the pharmacist simultaneously, a prescription by brand name and an authorization to fill it with a different brand, the authority of the pharmacist would be the sum of the two authorizations. The situation is precisely the same with respect to a brand name pre-

4. The American Law Institute states as a general rule that "words or other manifestations of intention *** are given the meaning which the party making the manifestations should reasonably expect that the other party would give to them." Restatement, Law of Contracts (1932), sec. 233. Even in the unlikely event (*id.*, sec. 228) that the parol evidence rule were held applicable to a prescription, the document would still be interpreted in accordance with its meaning to "a reasonably intelligent person acquainted with all operative usages and knowing all the circumstances" (ruling out only oral statements by the parties of what they meant). *Id.*, sec 230.

5. 9 Wigmore, Evidence (3rd ed., 1940), sec. 2463; 3 Williston, Contracts (rev. ed., 1936), sec. 608; 3 Corbin, Contracts (1951), sec. 555. The American Law Institute states that a usage is effective where the parties have agreed to it, or where they know of its existence and neither party "knows or has reason to know that the other party has an intention inconsistent with the usage. "Restatement, Law of Contracts, sec. 247.

The Institute gives this highly pertinent illustration (*id.*, sec. 246, illustration 3): A contract to sell "San Domingo mahogany" may be fulfilled, in accordance with a usage of the trade, by the delivery of mahogany of similar characteristics but of different origin. By the same token, it seems clear, an order for a proprietary drug may be filled, in accordance with a hospital usage, by the delivery of a drug chemically and therapeutically identical but of different origin.



MASON, FENWICK & LAWRENCE
Patent and Trade-Mark Lawyers
Woodward Building, 15th & H Streets, N.W.
Washington 5, D.C.

May 17, 1960

Mr. Alanson W. Willcox
General Counsel
American Hospital Association
Mills Building
17th and Pennsylvania Avenue, N.W.
Washington 6, D.C.

Dear Alan:

This will acknowledge your letters of April 21st, May 2nd and May 10th, 1960 regarding the application of the formulary system with respect to prescribing and dispensing of drugs in hospitals and confirm my conferences on May 2nd and 10th with you, Dr. Archambault, and G. Cabell Busick of our office regarding the matter.

We have reviewed the information furnished regarding the formulary system. It is our understanding that under this system physicians consent and agree that in prescribing or ordering a particular drug by a proprietary name, they authorize the hospital pharmacists to fill the prescription or order with the same drug, although it may be of different manufacture or source than that indicated by the prescription or order.

We also understand that in the event a physician desires that a drug of particular manufacture or source be dispensed, specific instructions over and above the designation of a proprietary name must be given by the physician. In the absence of specific instructions for the filling of the prescription or order with a drug of particular manufacture or source the pharmacist may fill the prescription or order with the same drug, but it need not be of the same manufacture or source as indicated by the proprietary name on the prescription or order.

We believe that when pursuant to a valid consent of the physician a prescription or order is filled by the pharmacist with the same drug, but of different manufacture or source, the container for which bears merely a non-proprietary name this would not constitute passing off nor would it impinge upon the trademark rights of the company whose proprietary name appears on the prescription or order. It is understood that the prescription or order in question is intended to be only a means of communication between the physician and the hospital staff pharmacist, both of whom have knowledge of and have undertaken to participate in the formulary system.

As further evidence of the physician's consent it is desirable where feasible for the prescription or order to bear a legend substantially as follows:

> **"Authorization is given for dispensing by non-proprietary name under formulary system unless checked here ———."**

Under such circumstances the physician has specifically authorized the pharmacist to fill the prescription or order by non-proprietary name in accordance with the rules of the formulary system to which he has agreed.

We have also considered the problem involved in the labelling of a drug for use in the hospital when the prescription or order is filled with the same drug but of different manufacture or source from that indicated by the proprietary name. If the actual contents are not those of the manufacturer or source whose proprietary name is designated on the prescription or order, use of the proprietary name on the label should preferably be avoided.

We understand, however, that it is essential in many instances that the proprietary name be placed on the label in some manner in order that the nurse administering the medication has a check against the prescription or order to avoid medication error. In such situations an appropriate legend must appear on the label in conjunction with the proprietary name. The legend should not state that the contents are those of the manufacture or source identified by the proprietary name when such is not the fact. A legend, such as the one suggested below, may suffice.

> (Non-proprietary name)
> **Note for information of nurses:**
> **Prescription or order for ———————————— filled by non-proprietary name as per formulary policy; contents may be of different source or identified by another brand name.**

The space in the legend would be completed by the pharmacist with the proprietary name which appeared on the prescription or order. If a legend along the lines suggested above is used, the staff and personnel, familiar with the formulary system, who administer the drugs should know that the contents, although of the same drug, are not necessarily of the same source or manufacture as identified by the proprietary name on the prescription or order.

Sincerely yours,
BOYNTON P. LIVINGSTON

BPL:hcm

scription accompanied by a prior general authorization, provided (1) that the authorization was valid in the first place, and (2) that it still subsists.[6]

1. We have seen that such a general authorization, probably valid in any case, is unquestionably valid if a mechanism is provided by which the physician may insist on a particular brand when he so desires.

2. In the case we are supposing, the authorization has not been revoked or rendered inapplicable to the particular case—and therefore it still subsists—unless the very act of writing a prescription in a proprietary name were held to constitute a revocation, either *in toto* or *ad hoc*. But the parties have agreed that this act shall not in itself be a revocation; they have agreed that something more than the writing of a trade name shall be necessary to render the general authorization inapplicable even to the particular case. With considerations of public policy fully satisfied by the physician's reserved right to insist upon a brand, there is no reason that a court should hesitate to respect the agreement of the parties on this point.[7]

Labeling of Medication Containers

So far as they relate to trademarks, questions of labeling are dealt with in the accompanying opinion of Mr. Livingston. The same precautions which he finds sufficient to preclude trademark infringement should suffice to prevent formulary nomenclature from raising any question of false labeling under food and drug laws.

Any labeling requirement under food and drug or similar laws, other than with respect to the naming of the drug, will presumably be unaffected by the formulary system. So far as nomenclature is concerned, an accurate use of the nonproprietary name is both unobjectionable and, as far as is known, everywhere legally sufficient. Use of a proprietary name which corresponds to the actual contents is also unobjectionable.

If as a safeguard against medication error a proprietary name appearing on the prescription also appears on the label in conjunction with the nonproprietary name, but does not correspond to the contents, it is essential that a format be employed which clearly negates any inference that the proprietary name describes the contents. Suitable formats are suggested in the guiding principles and in Mr. Livingston's opinion.

Some hospitals have adopted the practice in these cases of putting on the label the nonproprietary name and of following it, in parentheses but without explanatory wording, with the proprietary name which appears on the prescription even though the contents are of a different brand. This practice cannot be approved. Such labeling is inherently deceptive, and it is not a safe or sufficient answer (though it is a true one) to say that hospital personnel familiar with the formulary system will not be deceived. If a container so labeled were produced in court, it would be difficult to persuade the judge that deception was not threatened, however unintentionally. The risk of an adverse ruling is too great to be warranted.

The guiding principles state that the suggested form of labeling may be adapted for use on nursing station medication containers. Here the problem is a little different, since it may involve a number of brand names in which prescriptions for the basic drug may be written. A suitable adaptation would be:

> *(Nonproprietary Name)*
> Note for information of staff: Contents may be used, per formulary policy, to fill prescriptions or orders for any of the following brands of the same basic drug:
> *(Proprietary Name, Brand No. 1)*
> *(Proprietary Name, Brand No. 2)*
> *(Proprietary Name, Brand No. 3)*

So far as possible, the proprietary names of all brands of the basic drug should be listed; at least all those names used by the hospital staff in prescribing the basic drug.

Conclusion

The hospital formulary system would present no basic legal problem if all prescriptions were written in official or nonproprietary names.

To enable prescriptions written in proprietary names to be filled without regard to brand requires the authorization of all those who write such prescriptions. The risk of disciplinary proceedings against the pharmacist, the risk of criminal liability on his part and perhaps on others', and the risk of complication in civil litigation are too great to permit the slighting of legal niceties.

The system outlined in the guiding principles, in the opinion of the present writer, meets the requirements of federal law, and probably the requirements of most if not all state laws. For advice on compliance with state laws, however, state hospital associations or individual hospitals must look to local counsel. The initiation of a formulary system without adequate legal advice is a hazardous undertaking.

6. State laws forbidding substitution without the consent of the prescriber would seem to be satisfied if the same two conditions are met—that the consent was valid when given, and that it still subsists.

7. Compare the rule that acts, which would otherwise constitute a waiver of a term of a contract, do not constitute a waiver if the parties have agreed that they should not. As Professor Williston says: "*** when the parties have expressly agreed, whether orally or in writing, that certain acts otherwise ambiguous shall not be taken to have a certain meaning, that meaning should not be attributed to them." Williston, op. cit., sec. 765.

statement of

GUIDING PRINCIPLES ON THE OPERATION OF THE HOSPITAL FORMULARY SYSTEM

Approved by the Board of Trustees of the American Hospital Association and the Executive Committee of the American Society of Hospital Pharmacists August 1960

Preamble

► HOSPITALS MARSHAL AND ORGANIZE the best professional skills and judgment available to provide care and treatment of patients. The treatment of these patients in many cases is dependent upon the effective use of drugs. The multiplicity of drugs available makes it mandatory that a sound program of drug usage be developed within the hospital to ensure that patients receive the best care and protection possible.

In the interest of better patient care, hospitals and their medical staffs have advocated a program of objective evaluation, selection and use of medicinal agents in the hospital. This program is the basis of rational drug therapy in hospitals and has been utilized is an accepted method of providing a program of rational drug therapy in hospitals and has been utilized as such over the years by physicians, administrators and pharmacists.

A valid hospital formulary program is based upon its approval by the organized medical staff, the consent of individual staff members, the functioning of a properly motivated Pharmacy and Therapeutics Committee[1] of the medical staff, and upon acceptance of the use of nonproprietary terminology. The Pharmacy and Therapeutics Committee, composed of physicians and a pharmacist and selected under the guidance of the medical staff, represents the official organizational line of communication and liaison between the medical staff and the pharmacy department. The committee is responsible to the medical staff as a whole and its recommendations are subject to approval by the organized medical staff, as well as to the normal process of administrative approval. This Committee assists in the formulation of broad professional policies relating to drugs in hospitals, including their evaluation or appraisal, selection, procurement, storage, distribution, use and safety procedures.

Definition of Hospital Formulary and Hospital Formulary System

The hospital *formulary* is a compilation of pharmaceuticals which reflects the clinical judgment of the medical staff; it is under continuous revision to keep it current.

The hospital formulary *system* is the accepted method whereby the medical staff of a hospital, working through a Pharmacy and Therapeutics Committee selected by it, evaluates, appraises and selects from among the numerous medicinal agents available those that are considered most useful in patient care, together with the pharmaceutical preparations in which they may be administered most effectively. With prior consent of individual members of the organized medical staff, the hospital formulary system provides for the procuring and prescribing of drugs under either their nonproprietary or proprietary names in instances where drugs have both names, although the nonproprietary designation is preferred and stressed and is used in dispensing and administering. Under the formulary system, the medical staff member agrees that when he prescribes by proprietary name he is (unless he otherwise indicates) authorizing the hospital pharmacist to dispense and the nurse to administer the same drug under its nonproprietary name irrespective of whether it is or is not of the same brand referred to in the prescription or order.

Guiding Principles

The following principles may serve as a guide to physicians, administrators and pharmacists in hospitals operating with the formulary system.

1. The medical staff should appoint a Pharmacy and Therapeutics Committee composed of physicians and the pharmacist and outline its purposes, organization, function and scope.

2. The formulary system is a creation of the medical staff based upon the recommendations of the Pharmacy and Therapeutics Committee. The medical staff should adapt the principles of the formulary system to the needs of the particular hospital.

3. The medical staff should adopt written policies and procedures governing the formulary system as developed by the Pharmacy and Therapeutics Committee. Action of the medical staff is subject to the normal process of administrative approval.

[1]Statement on Pharmacy and Therapeutics Committee, adopted by the Board of Trustees of the American Hospital Association and the Executive Committee of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS in February 1959.

These policies and procedures should afford guidance in the evaluation or appraisal, selection, procurement, storage, distribution, use, safety procedures, and other matters relating to drugs in the hospital and should be published in the hospital's formulary or other media available to all members of the medical staff.

4. The medical staff should adopt the policy of, and formulate the procedure for, including drugs in the formulary and dispensing of such drugs by their nonproprietary names, even though brand name drugs are and will continue to be in common use in the hospital. The writing of prescriptions and medication orders by their nonproprietary names is preferred, although not required as a universal practice.

5. The institution of a hospital formulary system may be accomplished in any of several ways. Regardless of the method selected, it is essential that the consent of each person who is authorized to write a prescription or medication order, including house officers, be obtained in writing so that the hospital may prove such consent. However expressed, the consent is to be effective except as the prescriber otherwise indicates.

The following methods are suggested:

a. Basic policies and procedures governing the formulary system may be incorporated in the medical staff by-laws, or in the medical staff rules and regulations. Thus, each physician, upon accepting an appointment or reappointment to the hospital medical staff, gives prior consent to the formulary system in signing an appropriately worded agreement to abide by the by-laws, rules and regulations. House officers not required to sign the by laws should execute separate consent agreements.

b. Consent may be expressed in a separate document signed by all of the physicians.

c. Consent may be expressed by the use of a suitable worded imprint on hospital prescription and medication order forms, which evidences the consent of the prescriber each time he writes a prescription order.

6. A hospital should make certain that its nursing personnel are informed in writing (through its established means of communication) about the existence of the formulary system in the hospital and the procedures governing its operation.

7. In the formulation of policies and procedures, the terms "substitute" and "substitution" should be avoided, since these terms have been used to imply the *unauthorized* dispensing of a brand different from that prescribed or the dispensing of an entirely different drug, neither of which takes place under a properly operated formulary system.

8. Provision should be made to apprise the medical staff of changes in the working of the formulary system or in the content of the hospital formulary.

9. Provision should be made for the appraisal and use by members of the medical staff:

a. of drugs not included in the formulary

b. of investigational drugs[2]

10. The pharmacist, with such advice and guidance from the Pharmacy and Therapeutics Committee as may be indicated, should be responsible for specifications as to quality, quantity, and source of supply of all drugs, chemicals, biologicals and pharmaceutical preparations used in the diagnosis and treatment of patients, and for assuring that quality is not compromised for economic considerations. Such products shall meet the standards of quality of the United States Pharmacopeia, National Formulary, New and Nonofficial Drugs, Accepted Dental Remedies, or other accepted national standards.

11. The labeling of a medication container with the nonproprietary name of the contents is always proper. The use of a brand name other than that describing the actual contents is improper if it is used in a manner that can be taken as descriptive of the contents, even though personnel familiar with the formulary system may understand that it is not descriptive.

The following format is recommended for labeling individual patient's containers used within hospitals:

(Nonproprietary Name)
Note for information of staff:
Prescription or order for
(Proprietary Name)
filled as per formulary policy; contents are same basic drug as prescribed but may be of another brand.

The above format can be adapted for use in labeling nursing unit medication containers listing commonly used proprietary names.

12. In the absence of written policies approved by the medical staff relative to the operation of the formulary system, the pharmacist must dispense the brand prescribed, bearing in mind his professional prerogative to confer with the physician should the prescribed brand be unavailable. Also, where a formulary system has been adopted, provision should be made for the exercise of a physician's professional prerogative in those cases where he believes a specific brand of a drug is important to the care of his patient, and so designates in a manner approved by the medical staff (other than by writing the brand name alone).

Recommendation

A formulary system, based upon these guiding principles, is considered to be essential in the promotion of a rational drug therapy program in hospitals. In the interest of better patient care, its adoption by hospital medical staffs is recommended.

[2]Statement of Principles Involved in the Use of Investigational Drugs in Hospitals, adopted by the Board of Trustees of the American Hospital Association in September 1957, and approved by the Executive Committee of the American Society of Hospital Pharmacists in June 1958.

statement on the

PHARMACY & THERAPEUTICS COMMITTEE

Approved by the American Hospital Association and the American Society of Hospital Pharmacists, 1959

Preamble

► HOSPITALS ORGANIZE AND MARSHAL the best professional skills and judgment available to provide care and treatment of patients. The treatment of these patients in many cases is dependent upon the effective use of drugs. The multiplicity of drugs available today makes it mandatory that an organized sound program of activity be developed within the hospital to insure that patients receive the best care and protection possible.

One of the most effective ways of providing this kind of care and protection is by organizing a Pharmacy and Therapeutics Committee. This committee is designed to make maximum use of available professional skills and judgment. The establishment of a Pharmacy and Therapeutics Committee is strongly recommended to all hospitals. It is a measure which supports and enhances the principle of self-government in the area of high drug standards and practices for the medical staff connected with a hospital. Ultimate benefits accrue to the patient in improved patient care and treatment as established voluntarily by the medical staff.

The Pharmacy and Therapeutics Committee

The Pharmacy and Therapeutics Committee is an advisory group of the medical staff and serves as the organizational line of communication or liaison between the medical staff and the pharmacy department. This committee is composed primarily of physicians and the pharmacist and is selected under the guidance of the medical staff. It is also a policy-recommending body to the medical staff and to the administration of the hospital on all matters related to the use of drugs. (This committee does not have intrinsic authority or power of action unless specifically granted such authority.)

The above Statement on the Pharmacy and Therapeutics Committee was approved by the American Hospital Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS in 1959. It has been published in the March (1959) issue of the AMERICAN JOURNAL OF HOSPITAL PHARMACY and is reprinted here for convenient reference.

PURPOSES

The primary purposes of the Pharmacy and Therapeutics Committee are:

A. Advisory. The committee recommends the adoption or assists in the formulation of broad professional policies regarding evaluation, selection, procurement, distribution, use, safe practices, and other matters pertinent to drugs in hospitals.

B. Educational. The committee recommends or assists in the formulation of programs designed to meet the needs of the professional staff (doctors, nurses and the pharmacist) for complete current knowledge on matters related to drugs and drug practices.

ORGANIZATION

While the composition of the Pharmacy and Therapeutics Committee may vary from hospital to hospital, the following is offered as a guide:

A. The Pharmacy and Therapeutics Committee of the medical staff should be composed of no less than three physicians and the pharmacist, appointed by a governing unit or elected official of the organized medical staff. The hospital administrator or his designated representative should be an ex officio member of the committee.

B. A chairman from the physician representatives should be appointed. The pharmacist is generally designated secretary.

C. The Pharmacy and Therapeutics Committee should meet regularly, no less frequently than twice per year, and should meet on call when necessary.

D. The committee should feel free to invite to its meetings persons within or without the hospital who can contribute from their specialized knowledge or experience.

E. An agenda is desirable and should be prepared and submitted to members of the committee in sufficient time before the meeting.

F. Minutes should be kept by the secretary and should be maintained in the permanent records of the hospital.

G. Recommendations of the Pharmacy and Therapeutics Committee shall be presented to the medical staff or its appropriate committee for adoption or recommendation.

FUNCTIONS AND SCOPE

The basic organization of the hospital and medical staffs will determine the functions and scope of the Pharmacy and Therapeutics Committee. The following list, which is not necessarily comprehensive, is offered as a guide:

A. To serve in an advisory capacity to the medical staff and hospital administration in all matters pertaining to the use of drugs.

B. To serve in an advisory capacity to the medical staff and the pharmacist in the selection or choice of drugs which meet the most effective therapeutic quality standards.

C. To evaluate objectively clinical data regarding new drugs or agents proposed for use in the hospital.

D. To prevent unnecessary duplication of the same basic drug or its combinations.

E. To recommend additions and deletions from the list of drugs accepted for use in the hospital.

F. To develop a basic drug list or formulary of accepted drugs for use in the hospital and to provide for its constant revision.

G. To make recommendations concerning drugs to be stocked in hospital patient units or services.

H. To establish or plan suitable educational programs for the professional staff on pertinent matters related to drugs and their use.

I. To recommend policies regarding the safe use of drugs in hospitals, including a study of such matters as investigational drugs, hazardous drugs, and others.

J. To study problems involved in proper distribution and labeling of medications for inpatients and outpatients.

K. To study problems related to the administration of medications.

L. To review reported adverse reactions to drugs administered.

M. To evaluate periodically medical records in terms of drug therapy.

statement of

PRINCIPLES INVOLVED IN THE USE OF INVESTIGATIONAL DRUGS IN HOSPITALS

Approved by the American Hospital Association and the American Society of Hospital Pharmacists, 1957

► HOSPITALS ARE THE PRIMARY CENTERS for clinical investigations on new drugs. By definition these are drugs which have not yet been released by the Federal Food and Drug Administration for general use.

Since investigational drugs have not been certified as being for general use and have not been cleared for sale in interstate commerce by the Federal Food and Drug Administration, hospitals and their medical staffs have an obligation to their patients to see that proper procedures for their use are established.

Procedures

Procedures for the control of investigational drugs should be based upon the following principles:

1. Investigational drugs should be used only under the direct supervision of the principal investigator who should be a member of the medical staff and who should assume the burden of securing the necessary consent.

2. The hospital should do all in its power to foster research consistent with adequate safeguard for the patient.

3. When nurses are called upon to administer investigational drugs, they should have available to them basic information concerning such drugs — including dosage forms, strengths available, actions and uses, side effects, and symptoms of toxicity, etc.

4. The hospital should establish, preferably through the pharmacy and therapeutics committee, a central unit where essential information on investigational drugs is maintained and whence it may be made available to authorized personnel.

5. The pharmacy department is the appropriate area for the storage of investigational drugs, as it is for all other drugs. This will also provide for the proper labeling and dispensing in accord with the investigator's written orders.

The above Statement of Principles Involved in the Use of Investigational Drugs in Hospitals was approved by the American Hospital Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACIST in 1957. It has been published in the March (1958) issue of the AMERICAN SOCIETY OF HOSPITAL PHARMACY and is reprinted here for convenient reference.

ETHYLENE OXIDE STERILIZED PARENTERAL OLIVE OIL EMULSION

by E. MENCZEL, M. RABINOVITZ *and* A. MADJAR

► THE CLINICAL USES OF PARENTERAL EMULSIONS are expanding steadily. Intravenous emulsions of oil of chaulmoogra have been recommended in the treatment of leprosy.[1] Solutions of fat-soluble vitamins in oils can be emulsified for parenteral administration,[1] including the venous route. The intravenous infusion of finely dispersed cottonseed oil emulsion is reputed as highly effective for parenteral alimentation,[2] particularly in post-surgical treatment.

The accepted method of sterilization for parenteral emulsions consists of saturated steam at 15 lb./inch^2 for 30 minutes, commonly known as autoclaving.[3] The drawbacks of this thermosterilization method are: (1) impairment of the stability of the emulsion by reduction of viscosity and enhancement of coalescence of the globules and (2) decomposition of thermolabile oily constituents, solutes and emulsifying agents.

Cold Sterilization of Emulsions

Cold sterilization of intravenous oil emulsions should preferably replace thermosterilization provided it is effective, safe and uncomplicated. Bruno and Wilson and others have described cold sterilization of aqueous solutions by ethylene oxide. The method of Bruno and Wilson offers the advantage of using safely ethylene oxide in its cooled liquid form. Owing to miscibility of ethylene oxide with oils, this sterilization method was efficiently adapted for vegetable and mineral oils.[8] This simple sterilization method might be carried out at any hospital pharmacy without any particular facilities. The application of ethylene oxide sterilization for parenteral emulsions was evaluated experimentally on olive oil emulsions formulated for intravenous use.[9]

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Received from the Department of Pharmacy, School of Pharmacy, Hebrew University, Jerusalem and the Bacteriological Laboratory, Hadassah Hospital, Tel-Aviv. We acknowledge gratefully the assistance given by Professor E. Fisher in carrying out this study. The animal tests were conducted by N. Khazan Ph.D. and Kelmar M.D.

Materials and Reagents

1. Ethylene oxide: liquid ampul kept in a thermos bottle containing a water-ice mixture at 1°C. and, through its stopper, a glass tube (3 mm. in diameter) was inserted and filled with glass wool to serve as a safety vent. The ethylene oxide was removed from the ampul through a pipette fitted with a small rubber bulb to avoid inhalation of ethylene oxide. All dilution manipulations were carried out at about 1° C. and the sterile pipettes were precooled in a refrigerator. It should be noted that electric refrigeration is inadvisable owing to inflammability and explosion hazards.
2. Castor Oil U.S.P. and Olive Oil U.S.P.: both oils were neutralized according to the method of the French Pharmacopoea;[10] acidity was less than 0.08 percent free acid.
3. Liquid Petroleum U.S.P. (Mineral Oil)
4. Glyceryl monostearate: self-emulsifying grade.
5. Sodium chloride solution, 0.9 percent, sterilized at 15 lb./inch^2 (121° C.) for 30 minutes.
6. Dextrose injection 5 percent w/v.
7. Water for Injection U.S.P.
8. Bacteriological media: (1) Bacto-bouillon peptone 1.0 Gm., sodium chloride 0.5 Gm., beef extract 0.5 Gm., purified water to make 100 ml., *p*H adjusted to 7, and sterilized at 15 lb./inch^2 (121°C.) for 30 minutes. (2) Bacto-Sabouraud maltose agar: neopeptone-Difco 10 Gm., maltose Difco 40 Gm., Bacto agar 15 Gm., water to make 1000 ml., *p*H adjusted to 5.6 and sterilized at 15 lb./inch^2 (121°C.) for 30 minutes.
9. Microörganisms: *B. subtilis, E. coli* and *S. aureus.*

Preparation and Physical Properties of Parenteral Olive Oil Emulsion

The parenteral olive oil emulsion formulated by the method of Lerner *et al.*,[9] consisted of olive oil (neutralized) 10 Gm., glyceryl monostearate 5.0 Gm., dextrose injection (5 percent) to make 100 ml. It was prepared by pressure homogenization but its physical properties were not reported. The hydrophile-lipophile balance (HLB) of glyceryl monostearate S.E. is 5.5[12]; it is a blend[13] just suitable for oil-in-water emulsions. We have prepared this emulsion by four different methods: (1) continental mortar and pestle method (emulsion I), (2) pre-mixing in an electric stirrer and dispersed by a Waring blender* (emulsion II), (3) pre-mixing in an electric stirrer and pressure homogenization using

an electric Gann Emulgor I** (Emulsion III), (4) mixing and homogenization by ultrasonic waves using Minisonic homogenizer*** (Emulsion IV).

The plastic viscosities of the resulting emulsions, as determined by Brookfield synchrolectric viscometer model LVT, are quite different. The least viscous emulsion is that produced by pressure homogenization (see Table 1 and rheograms of Figure 1). However, increasing the rate of shear and/or augmenting the temperature reduce the differences in the viscosities, particularly of the mechanically prepared emulsions. At 1.5 r.p.m., 10°C. the viscosities of emulsion II and IV were 11200 c.p. compared with 8800 c.p. of emulsion III at the same conditions, whereas at 60 r.p.m., 40°C. the values were: emulsion II 800 c.p., emulsion IV 900 c.p. and emulsion III 600 c.p.

Even at increased temperature and rate of shear the highest viscosity is produced by the hand prepared emulsion: at 60 r.p.m., 40°C., values were 1500 c.p. for emulsion I compared with 600 c.p. for emulsion III. It appears that the higher viscosity of the hand prepared emulsion is a function of the coarseness of the dispersion. The degree of dispersion of the emulsion prepared by the mechanical methods appears to be alike according to microscopic examination using an erythrocytes micrometer. The diameter of the dispersed globules was found to be between 0.5 and 2 microns. On the other hand, the dispersion of the hand prepared emulsion was quite coarser.

The *p*H of the four types of this emulsion determined at 20°C. using a Beckman *p*H model H2 varied slightly: emulsion I was 8.2, emulsion II was 8.2, emulsion III was 8.9, and emulsion IV was 8.15. Since the *p*H of 5 percent aqueous glyceryl monostearate solution (jelly) was found to be 8.6, the alkalinity appears to be due to the sodium stearate present in glyceryl monostearate S.E. grade.[11] The sequence of these emulsions stabilities determined at exponential intervals, was as follows: emulsion III>emulsion>I emulsion>IV emulsion II. We could confirm that the least viscous emulsion prepared by homogenization is stable for three months whereas it should be noted that the emulsion prepared by Waring blender was unstable at one month.

It was therefore concluded that emulsion III is the most satisfactory preparation and thus further tests were carried out only with it.

Sterilization and Sterility Testing

The olive oil emulsion was precooled to 3-5°C. and liquid ethylene oxide was added to give a concentration of 1 percent. The emulsion was kept at this low temperature for one hour during which active sterilization takes place. Sterility was tested by centrifuging

*Waring Products Corporation, New York.
**Gann, Stuttgart, Germany
***Ultrasonic Ltd. Otley, Yorks, England

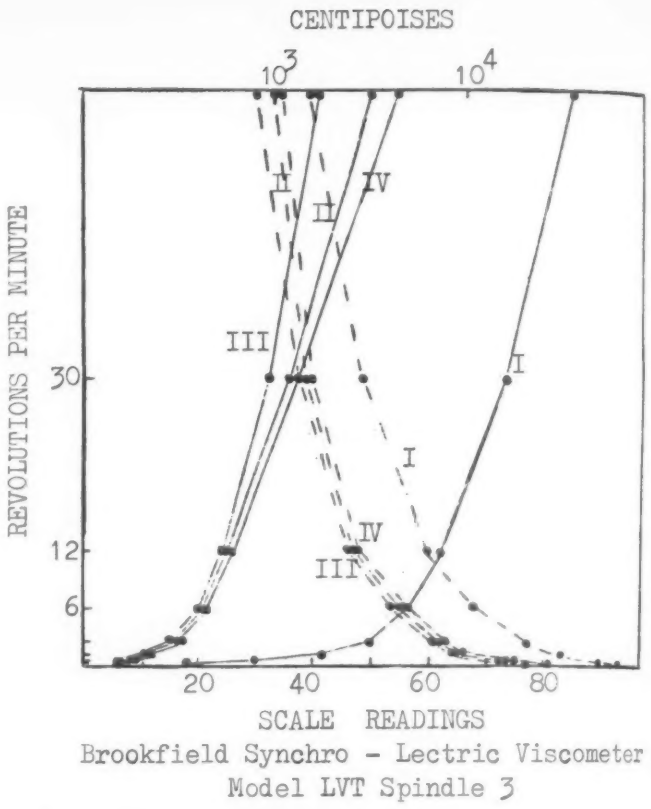

Fig. 1. - Rheogram of parenteral olive oil emulsion prepared by I - hand, II - blender, III - pressure homogenizer, IV - ultrasonic homogenization.

———— Slope of shearing stress (scale readings) upon increasing or decreasing rate of shear (revolutions per minute).

— — — — — Slope of apparent viscosity (centipoises - semilog. scale) upon increasing or decreasing rate of shear (r.p.m.).

10 ml. of the test emulsion at 3000 r.p.m. for 10 minutes, the supernatant broken emulsion liquid was poured off and the remaining two or three drops were added to 5 ml. of bouillon, after which two or three additional drops were streaked on the Sabouraud medium. The bouillon was incubated for 24 hours and the Sabouraud medium for four days. After incubation, the inoculated media were examined for growth. Sterility was indicated by the absence of growth. The same results were obtained in the duplicate set at the same time, and upon repeating these tests five times at intervals of several days. Blank controls were run simultaneously.

Intravenous Infusion to Rabbits and Dogs

The least viscous parenteral olive oil emulsion (emulsion III), sterilized by the method described above and proved to be sterile, was administered by infusion to rabbits and dogs. Three rabbits were anesthetized by the injection of pentobarbital sodium receiving 2 to 3 ml. at the rate of one ml./minute. Diluting the test emulsion with equal parts of dextrose injection 5 percent and administering the resulting dilution to rabbits at a rate of 0.2 ml. per minute proved to be entirely satisfactory. A 20 ml. dilution of the olive oil

Table 1. Apparent Viscosities* Upon Increasing Rate of Shear and Temperature of Parenteral Olive Oil Emulsion Prepared by Different Methods.

Emulsion	Temperature Centigrades	Revolutions per Minute 0.3	0.6	1.5	3	6	12	30	60
I	10°	80000	64000	34400	20800	11600	6500	3040	1800
	20°	72000	60000	33600	20000	11200	6200	2920	1700
	30°	60000	56000	32000	18800	10800	5800	2800	1600
	40°	48000	50000	30400	18000	10400	5500	2720	1500
II	10°	28000	20000	11200	7200	4400	2800	1520	1100
	20°	20000	16000	8800	6400	4000	2500	1440	1000
	30°	16000	14000	8000	5600	3600	2400	1320	900
	40°	12000	10000	6400	4800	3200	2200	1200	800
III	10°	28000	20000	8800	6800	4400	2600	1440	900
	20°	20000	14000	7000	6000	4000	2400	1320	800
	30°	16000	12000	6400	4800	3600	2300	1280	700
	40°	12000	10000	4800	4400	3200	2100	1200	600
IV	10°	32000	22000	11200	8000	4800	3000	1600	1200
	20°	28000	18000	9600	7200	4400	2700	1520	1100
	30°	24000	16000	8000	6400	4000	2500	1400	1000
	40°	20000	12000	6400	5600	3600	2200	1320	900

*Apparent viscosities in centipoises determined by Brookfield viscometer model LVT spindle 3.

Emulsion I was hand prepared; emulsion III was pressure homogenized; emulsion II was prepared by use of a blender; emulsion IV was homogenized by use of ultrasonics.

emulsion was administered repeatedly to rabbits weighing about 2 Kg. without any ill effects. The rate of intravenous infusions to dogs was far higher than that for rabbits, and it could reach up to 5 ml. per minute. No harmful effects could be observed following the intravenous administration of 100 ml. of dilution to each of two dogs weighing about 15 Kg.

Discussion

A parenteral olive oil emulsion was effectively cold-sterilized by ethylene oxide and was infused in dogs and rabbits. The olive oil emulsion was that originally formulated by Lerner *et al.*[9] who found that, after autoclaving, it could be administered safely to dogs. No comparison could be made with cottonseed oil emulsion of the N.N.D.[2] since its composition was not disclosed. The comprehensive study of Tober and Autian on coconut oil emulsion formulations[17] does not imply the feasibility of intravenous infusion of the suggested stable emulsions. Furthermore, there are other factors involved in parenteral emulsions in addition to those of formulation. Depending on the method of preparation of the parenteral olive oil emulsion studied, different plastic viscosities could be produced (Figure 1, Table 1) most of which are too high for intravenous administration. In this case, only the pressure homogenized emulsion yielded a free-flowing emulsion which did not block needles and the drip bulbs of infusion sets.

The concentration of 1 percent v/v ethylene oxide for sterilization of the emulsion is based on our findings summed up in Table 2. Purified water, sodium chloride solution, and bouillon were contaminated with *E. coli* by the standard procedure. A procedure was developed for similarly contaminating *E. coli* with a vegetable oil and a mineral oil respectively, having no self-steriliza-

Table 2. The Sterilizing Concentrations of Ethylene Oxide for Aqueous and Oily Media Contaminated with E. Coli.

Ethylene Oxide Concentration Percent v/v	Purified Water	Saline	Bouillon	Castor Oil	Liquid Petrolatum
0.5	—	—	—	—	—
0.4	—	+	+	—	—
0.3	+	+	+	—	—
0.1	+	+	+	—	—
0.04	+	+	+	—	—
0.036	+	+	+	+	—
0.033	+	+	+	+	—
0.030	+	+	+	+	+

+ Denotes growth of microörganisms

— Signifies absence of growth of microörganisms

tion properties, *i.e.* castor oil and liquid petrolatum.[8] The number of microörganisms per ml. of contaminated aqueous amd oily media was 4 x 10.[9] Ethylene oxide was added according to the prescribed procedure in descending concentrations starting with 0.5 percent v/v. The oily media were rendered sterile at 0.036 percent v/v ethylene oxide, whereas sterilization of the aqueous media was effected only at 0.5 percent v/v ethylene oxide. The same results were obtained with *B. subtilis* and *S. aureus*. Our results indicate that the recommended concentration of 1 percent ethylene oxide[4] for the cold sterilization of aqueous media includes a considerable excess as a wide margin of safety. It is obvious that this concentration should be adopted as well for the sterilization of o/w emulsions where the aqueous phase predominates. Sterility tests proved that the described sterilization method destroyed efficiently all the microörganisms present in the emulsions. Parenteral oil emulsions to which were added cultures of *B. subtilis, E. coli* and *S. aureus* were also rendered sterile by the suggested sterilization method, according to described sterility tests.

The residual ethylene oxide of the cold sterilized olive oil emulsion could not have been tested by the phenolphthalein method nor by the potentiometric method. The alkalinity of glyceryl monostearate affects both phenolphthalein and the potentiometric procedure. However, the residual ethylene oxide could be determined potentiometrically on the blank purified water and blank olive oil sterilized by ethylene oxide. It was found that 0.03 percent v/v ethylene oxide is still retained by the blank,[5] which ought to be equivalent to that of the sterilized parenteral olive oil emulsion at the same conditions. The toxicity of such a concentration was tested on albino rats which received for a month duration, daily injections of 0.3 ml./100 Gm. of sterilized purified water containing 0.03 percent v/v ethylene oxide. Fluctuations in the body weights of control albino rats receiving equivalent doses of water for injection were similar to those of rats to which were administered the residual ethylene oxide. No other ill effects were observed.

Results of the sterility tests and trial intravenous infusions to rabbits and dogs indicate the validity and safety of liquid ethylene oxide for the sterilization of intravenous oil emulsions. These results warrant further controlled clinical trials on the investigated parenteral olive oil emulsion for its human application as an agent for intravenous alimentation according to the methods evolved by Mann *et al.*,[19] Forbes,[20] Hurber,[21] Mueller,[22] Kaley[23] and others.

Moreover, the cold sterilization method for the preparation of parenteral emulsions will permit the use of thermolabile emulsifying agents. Use of this method eliminates thermolability of the emulsifying agents. The choice of emulsifying agents thus could be based on the hydrophile-lipophile balance (HLB) and stability of the emulsion system, provided that these emulsifying agents are physiologically compatible with parenteral administration.

Summary

A simple and reliable cold sterilization method using liquid ethylene oxide for intravenous olive oil emulsion is described. Bacteriological tests of parenteral olive oil emulsions sterilized by ethylene oxide proved perfect sterility. Tests of the residual ethylene oxide, determined potentiometrically and its toxic effects tested biologically, failed to indicate any harmful concentration nor any ill effects. Thermolability of an emulsifying agent need not hamper its use in a parenteral emulsion formulation.

The pharmaceutical aspects of an intravenous olive oil emulsion formulation containing glyceryl monostearate indicate that pressure homogenization is invaluable. An olive oil emulsion homogenized by pressure and sterilized by ethylene oxide was successfully infused in rabbits and dogs. Clinical trials are to be attempted to investigate its human application for intravenous alimentation.

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POLYVINYL ALCOHOL PACKAGING

in hospital pharmacy

by PHILIP R. HUGILL

► POLYVINYL ALCOHOL*, P.V.A., IS A THERMOPLASTIC material that may introduce new packaging techniques in the pharmaceutical industry.

Premeasured portions of medications may be individually enclosed in P.V.A. film. At the prescribed time, the package would be dropped in an aqueous vehicle and the P.V.A. packaging material dissolved to prepare a solution or suspension of medication. P.V.A. in solution, no longer a package, now exhibits emulsification properties that will often result in a more homogeneous preparation.

This material is chemically an internally plasticized polyvinyl alcohol resin. It is prepared by the acid hydrolysis of polyvinyl acetate and processed by molding, extrusion, or solution coating.

P.V.A.'s most outstanding property is the fact that it is soluble in cold water. However, petroleum hydrocarbons, oils, fats and waxes have no effect upon P.V.A. film. It is also substantially unaffected by most esters, ketones, ethers, aliphatic and aromatic hydrocarbons and higher monohydric alcohols. The lower monohydric alcohols exhibit some solvent action, and aldehydes and certain other chemicals tend to insolubilize P.V.A. film. The film is also impervious to gases and stable in sunlight and artificial light.[1]

A package constructed of P.V.A. film may be printed to describe the contents and give directions for use. The thickness commercially available is 0.0015 and 0.002 inches[2]. P.V.A. film may be heat-sealed and is suitable for production packaging with an automatic pouch-former-filler-sealer.[3] The sealing temperature of this film is 230° F. and the sealing characteristics are similar to polyethylene.[1]

P.V.A. film must be handled under controlled relative humidity atmosphere because of the unique property of being water-soluble. P.V.A. does not produce skin sensitiveness and is not absorbed upon oral ingestion. However, its internal use has not yet been approved by the F.D.A.[1]

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The pharmaceutical industry could find this material extremely useful in packaging medications. Some applications that have already been made are in the packaging of caustic and poisonous items such as bleach for home laundry.[3,4,5] The operator need not touch the harmful contents and the working area is not contaminated by dust or spillage since the material is packaged in pre-weighed quantity.

Suggested possible future uses for this water-soluble film might be in the packaging of many bulk pharmaceutical preparations. A partial list could include oral radiopaques such as barium sulfate; enema ingredients like tannic acid powder, barium preparations, liquid petrolatum; dermatology medications such as cottonseed oil to be added to bath water; and chemicals for topical dressings.

Perhaps it might even be feasible to bring P.V.A. packaged products into sterile hospital areas by using a second outer package that could be opened to drop the sterile-prepared water-soluble package into the sterile solvent. Thus a solution could be prepared aseptically.

**Elvanol,* Dupont de Nemours & Co., Inc., Wilmington 98, Delaware.

Gelvatol, Shawinigan Products Corp., 350 Fifth Avenue, New York 1, N. Y.

Lemol, Borden Chemical Co., Div. of The Borden Co., 350 Madison Ave., New York 17, N. Y.

Moviol, Farbwerke Hoechest A. G. vormals Meister Lubigs and Bruning, FFm., Hoechest, Germany.

Resistoflex, Resistoflex Corp., Belleville 9, N. J.

Vinol, Colton Chemical Co., Div. Air Reduction Co., Inc., 1747 Chester Avenue, Cleveland 14, Ohio.

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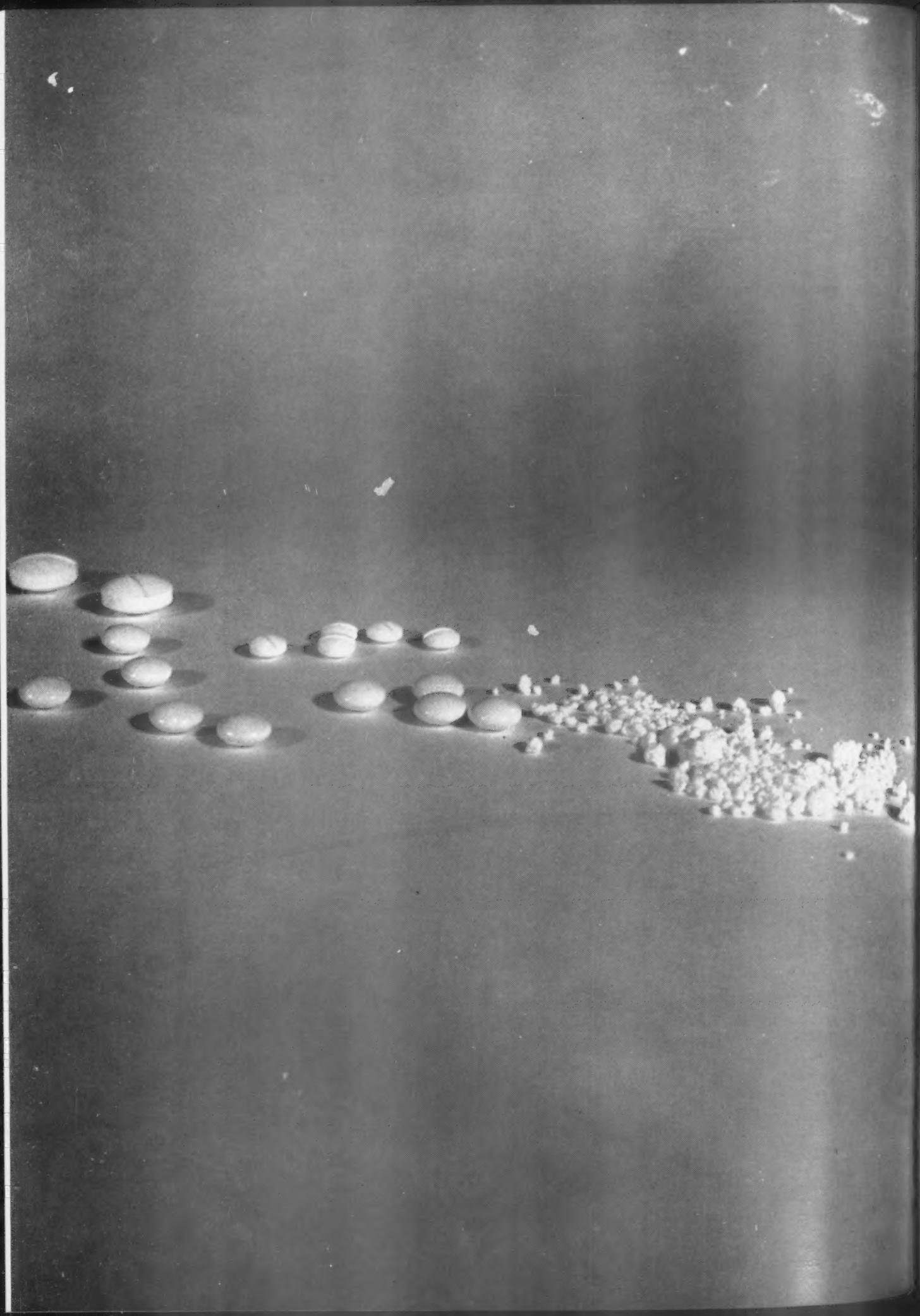

prevention of decomposition of medicaments due to EXCIPIENTS AND CONTAINERS

by T. D. WHITTET

► THE CHOICE OF THE BEST EXCIPIENTS FOR THE formulation of remedies is of vital importance in ensuring the stability and efficiency of the resulting preparations.

It is therefore essential that pharmacists should have as complete a knowledge as possible about all the chemical, physical and pharmacological properties of all substances used for the formulation of medicaments, including vehicles and excipients as well as those of the ingredients themselves. Although in Great Britain the term excipient is usually restricted to substances used in the formulation of tablets, capsules and pills, in this paper it has been taken to include any substance used in the formulation of a medicament.

Ideally one would not use as an excipient anything likely to cause decomposition of the medicament, but it is not always easy to ascertain whether any such effect is likely to occur. The field is so vast that it is not possible, in one paper, to cover more than some selected parts of it but I have endeavored to make the examples discussed deal with as wide a range of preparations as possible and have included as many personal observations as I can recollect.

I have also, in a few instances, taken a wide interpretation of the term "decomposition" and have included factors causing reduced efficacy or increased toxicity of medicaments which may not be due strictly to chemical decomposition. I have taken the view that anything which interferes with the effectivness or increases the danger of a medicine is as serious as actual decomposition of the active ingredient.

Since faulty packing or storage of medicines can invalidate the best formulated product, it is appropriate that the effect of containers on remedies should be discussed in the same paper.

As the earlier speakers in this symposium have dealt with the beneficial action of preservatives, antoxidants, solubilizing and suspending agents, etc., I shall confine my paper to examples where such substances have given unexpected and deleterious results.

To make the paper as precise as possible I have dealt first with the incompatibilities and factors causing instability of several important groups of drugs and with those of excipients used in many types of preparations. Subsequently examples of unexpected results of formulation are discussed under the heading of the particular type of pharmaceutical preparation.

A very extensive list of references is appended to the paper, since it is impossible to do more than mention some of the papers cited and the inclusion of all the references is therefore essential.

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General Incompatibilities of Some Important Groups of Drugs

Epinephrine and Related Substances

There have been many papers on the stability of adrenaline solutions and numerous incompatibilities have been reported. Girard and Kerney (1950) found that solutions stored in ampuls of certain kinds of yellow glass deteriorated rapidly because of the absorption of iron from the glass. Roscoe and Hall (1956) stated that ferric, ferrous, cupric and chromic ions catalyze the deterioration of adrenaline hydrochloride solutions and this can be prevented by chelating agents such as disodium hydrogen edetate.

Numerous workers have shown that sodium metabisulphite markedly retards the oxidation of adrenaline, but Schroeter *et al.* (1958) claimed that the degradation of adrenaline solutions in an oxygen-free atmosphere occurred more rapidly in the presence of 0.1 percent of sodium metabisulphite than in its complete absence. This, however, was only appreciable in neutral solution and there is no doubt that solutions of adrenaline tartrate or hydrochloride at a *p*H of about 3.4 to 4.0 are stable for many years (West 1950). There appear to be at least two independent reactions which can cause adrenaline destruction (West 1945). West (1952) found the conditions for nor-adrenaline stability to be very similar to those of adrenaline. In dilute solutions he reported greater stability in 5 percent dextrose solution, in distilled water, and in plasma than in saline and whole blood. Richards (1943) showed that metabisulphites increased the subcutaneous and intramuscular, but not the intravenous, toxicity of adrenaline, but West (1945a) found that this enhanced toxicity disappears on autoclaving solutions containing adrenaline and metabisulphite in full ampuls. The phenomenon does not appear to have any clinical significance.

Isoprenaline also has similar properties and stability to those of adrenaline. We have found that contact with metals in nebulizers causes marked discoloration and loss of activity.

Morch (1957) also studied the stability of adrenaline and nor-adrenaline solutions and noted the deleterious effects of traces of copper.

Antibiotics

With such a diverse and biologically active group of substances as the antibiotics it is not surprising that many incompatibilities have been reported.

Bacitracin. Plaxco and Husa (1956) showed that bacitracin is slowly inactivated in bases containing stearyl alcohol, cholesterol, polyoxyethylene derivatives, and sodium lauryl sulfate. It is rapidly inactivated in bases containing water, macrogols, propylene glycol, glycerin, cetylpyridinium chloride, benzalkonium chloride, ichthammol, phenol, and tannic acid. Nixon (1951) also reported rapid loss of activity in bases containing polyethylene glycol 4000 and propylene glycol. Bond *et al.* (1949) stated that bacitracin is unstable in aqueous ointment bases.

Chloramphenicol. Higuchi *et al.* (1954) reported that, although chloramphenicol is stable in solution over a wide range of *p*H, decomposition is catalyzed by monohydrogen phosphate and mono- and di-hydrogen citrate ions and by undissociated acetic acid.

Neomycin. Simone and Popino (1955) found that neomycin is very stable except that ointments in hydrous lanolin showed marked instability. Hill *et al.* (1955) reported that neomycin is incompatible with anionic substances. It becomes firmly bound to bentonite, cracks emulsions prepared with sodium lauryl sulfate and precipitates some gums from jellies such as carboxymethylcellulose. Price *et al.* (1957) found inorganic ions to be highly inhibitory to neomycin.

Penicillin. Many incompatibilities have been reported for penicillin—aminacrine hydrochloride, chlorbutol (Denston 1946); chlorocresol, parahydroxybenzoate, glycerin and propylene glycol (Johnson and Lerrigo 1947); traces of heavy metal ions such as mercury, copper and zinc, rancid oils (Berry 1946); wood alcohols, hard paraffin, macrogols, cetostearyl alcohol, self-emulsifying stearyl alcohol, cocoa butter, emulsifying wax, polychols, lanolin, crude cholesternated bases and many ionic and non-ionic surface active agents (Woodard 1952).

Kern *et al.* (1950) reported that penicillin deposits crystals of phenyl phenaceturate when preserved with phenol in a citrate buffer. Sherwood and Mattocks (1951) found that Carbowax 1000 and polyethylene glycol 600 inactivated penicillin in ointments.

I believe that I was the first to report the incompatibility of procaine hydrochloride and penicillin (Whittet 1946). This is an example of an incompatibility which has been made use of in pharmaceutical formulation.

Polymyxin. Newton (1953) reported that calcium, magnesium, manganese, and ferrous ions inhibit the action of polymyxin.

Streptomycin and Dihydrostreptomycin. Buckwalter (1954) stated that aqueous solutions of streptomycin are stable between *p*H 3 and *p*H 7 but rapidly decompose in alkaline solution. On the other hand, Berkman *et al.* (1957) noted that streptomycin activity decreases with decreasing *p*H. They also found that sodium and potassium chlorides, sodium sulfate, Sorensen's buffer and ammonium acetate materially decrease the activity of streptomycin. Oswald and Nielsen (1947) gave *p*H 6 to 8 as the optimal range for stability. Price *et al.* (1957) reported inorganic ions, especially calcium and magnesium to be inhibitory. Buckwalter (1954) lists hydroxylamine hydrochloride as an inhibi-

tor of streptomycin and potassium permanganate, hydrogen peroxide, potassium iodide and chloride as incompatibilities.

It is well known that solutions of streptomycin and dihydrostreptomycin discolor on storage and that this can be prevented by the addition of buffers and sodium metabisulphite. In this hospital we found that buffered solutions cause considerably more pain than plain ones and, since it appears that discoloration does not indicate loss of activity or increase in toxicity, we use unbuffered injections. Vegt (1955) studied the stability of dihydrostreptomycin in aqueous solution and found that in some circumstances the use of succinic acid-borate buffer increased the rate of decomposition.

The Tetracyclines. The tetracyclines appear to be stable in aqueous solution only if the *p*H is appreciably acid. The stability of chlortetracycline has been studied by Harned *et al.* (1948) and oxytetracycline by Regna and Solomons (1950). Solutions of tetracycline and of oxytetracycline appear to be appreciably more stable than those of chlortetracycline. There is little difference between the stabilities of tetracycline and oxytetracycline.

Several workers have reported inhibitory effects of inorganic ions, especially divalent cations, on the tetracyclines. Weinberg (1953) showed that magnesium, manganese, ferrous, and ferric ions sharply depressed the action of chlortetracycline. In a later paper (1954-5) he included calcium among inhibitors. His findings for magnesium and calcium were confirmed by Price *et al.* (1957). Johnson and Colmer (1957) stated that magnesium inhibits chlortetracycline and Hamberger *et al.* (1956) showed that magnesium both inhibits tetracycline and causes a fourfold diminution in blood levels in human beings.

These incompatibilities, especially that of calcium, are important in the formulation of capsules and tablets.

Dony-Crotteux (1957) showed that riboflavin caused inactivation of the tetracyclines, oleandomycin, the streptomycins, tyrothricin, erythromycin and actinomycin C. The mechanism seemed to be photochemical oxidation and is prevented by antoxidants. The tetracyclines are most seriously affected. This again is important since antibiotics are sometimes formulated together with the vitamin B complex.

Vitamins

Thiamine (Aneurine) Hydrochloride. Martindale (1958) lists mercuric chloride, iodides, carbonates, acetates, ferric sulfate, tannic acid, ferric ammonium citrate, and sodium phenobarbitone as incompatible with aneurine hydrochloride. Partington and Waterhouse (1953) reported on the effect of various minerals on the stability of the vitamin in compound powders and uncoated tablets. They found that copper and cobalt, which are known to cause decomposition, are less likely to do so in the presence of phosphate and gluconate buffers. Magnesium carbonate caused increased decomposition. Control of *p*H and protection from oxidation are also important with this vitamin. Stuckey (1953) confirmed that iron causes decomposition. Stone (1950) reported that aneurine hydrochloride is more stable in oral multivitamin preparations as the water content increased and that the vitamin may react with sugars. Campbell and McLeod (1955) found that high concentrations of sulfite caused destruction of aneurine.

Nicotinic acid. The only incompatibility quoted by Martindale (1958) is with oxidizing agents. Schou (1957) found that this compound readily dissolves copper from vessels with loss of stability.

Riboflavin. According to Martindale this is incompatible with alkalis and salts of heavy metals. Brumfield and Gross (1955) reported that the calcium ion inactivates riboflavin and that certain metallic ions cause decomposition of riboflavin 5 phosphate.

Para-aminobenzoic acid. Solutions of the sodium salt of this vitamin are incompatible with ferric salts and oxidizing agents. They darken on exposure to light in the presence of air. I have found that the use of sodium metabisulphite or the replacement of air in ampuls by nitrogen will prevent this.

Folic acid. The incompatibilities of this vitamin were studied by Bergy (1950), who reported that in alcoholic solution it is incompatible with chloral hydrate, ferrous sulfate, sulfonamides, mucilage of acacia, soluble calcium salts, acidic vitamin preparations, and cherry and raspberry syrups.

Biamonte and Schneller (1951) examined the stability of folic acid in various solvents and in the presence of other members of the B vitamins. They found that it is stable in the presence of a citrate-phosphate buffer at *p*H 6.0 to 9.8, but at *p*H 5.0 or lower it has a low solubility and such solutions rapidly decline in potency. Considerable decomposition takes place in solutions containing riboflavin and somewhat less with aneurine hydrochloride. In aqueous media, at *p*H 3 to 4, however, because of its insolubility, folic acid is stable in the presence of all the vitamins of the B group. Among the vehicles tested in multivitamin preparations, samples containing propylene glycol showed the greatest amount of folic acid decomposition.

Scheindlin *et al.* (1952) also reported rapid decomposition of folic acid in the presence of riboflavin and light. It can be minimized by adjustment of *p*H to 6.5, exclusion of air and light, and the addition of antoxidants. Taub and Lieberman (1953) found that aminoacetic acid which has been used as a solvent for folic acid causes decomposition within a few weeks.


SOLUBLE
ANN ARBOR

Cyanocobalamin. Incompatibilities of this vitamin have been listed as follows: vitamin K diphosphate, ascorbic acid, fructose and dextrose (Bogash 1955), oxidizing and reducing agents, salts of heavy metals, strong acids or alkalis (Martindale 1958).

There have been many conflicting reports on the stability of cyanocobalamin in the presence of other vitamins. Blitz *et al.* (1954; 1956) reported that, at the optimum *p*H value of 4.5, vitamin B_{12} is not stable in the presence of both aneurine and nicotinamide although either of these vitamins separately did not cause decomposition. On the other hand, Feller and Macek (1955) found that, in the presence of aneurine and nicotinamide, cyanocobalamin was stable at *p*H 3.5 to 4.5 at room temperature but decomposed at 120°C. in the presence of aneurine or its breakdown products. The findings of Dony and Conter (1956) agree with those of Blitz *et al.* One of the most recent papers on this subject is that by Gambier and Rahn (1958), who showed that good stability of cyanocobalamin can be obtained in the presence of aneurine and nicotinamide if certain processing rules are observed.

Blitz *et al.* (1954) also examined the effect of ascorbic acid on the stability of cyanocobalamin and found that it is influenced by the presence of trace elements. As little as 0.1 part per million of copper caused appreciable destruction of cyanocobalamin. Manganese ions had a similar effect. These reactions, which occur only in the presence of ascorbic acid, can be prevented by the use of metal ion complexing agents. Hutchins *et al.* (1956) showed that cyanocobalamin is more stable than the other cobalamins in the presence of ascorbic acid. This is important since Baxter *et al.* (1953) have shown that conversion of cyanocobalamin to hydroxycyanocobalamin takes place readily in the usual *p*H range under the action of light. The D.A.T.S. Report (1959) states that cyanocobalamin may be decomposed by oxidation or reduction or hydrolysis. Kalletis (1957) showed that some antoxidants had a deleterious effect on this vitamin.

Bartilucci and Foss (1954) reported that the optimum *p*H for a preparation containing both ascorbic acid and cyanocobalamin is between 6 and 7. Tetrasodium edetate had a stabilizing action on ascorbic acid but, unless acidified, had a deleterious effect on cyanocobalamin. They also examined the suitability of a number of vehicles and stated that cyanocobalamin has questionable stability in high concentrations of propylene glycol and in vehicles containing glucose. Barr *et al.* (1957) also investigated several vehicles and found dextrose and sucrose both caused destruction of cyanocobalamin.

Ascorbic acid. This vitamin is a very reactive substance. Martindale (1958) lists ferric salts, oxidizing agents and salts of heavy metals, particularly copper, as being incompatible. It is well known that changes in *p*H have an important effect on stability.

Bandelin and Tuschhoff (1955) found that the use of vegetable gums to produce solutions of greater viscosity produced accelerated destruction of the vitamin, whereas propylene glycol, glycerin and sorbitol stabilized them.

Stone (1950), in his examination of the stability of multivitamin preparations, found that aneurine hydrochloride increased the discoloration of ascorbic acid and Trenner *et al.* (1950) reported an incompatibility between some samples of cyanocobalamin and ascorbic acid.

Blaug *et al.* (1958) studied the effect of various metallic ions in the sulfate form on the stability of ascorbic acid in tablets and placed them in the following order of effect in causing decomposition. Cu > Co > Mn > Zn > Fe. They also quote from Klodt and Steib (1938) that the presence of copper ions greatly increased oxidation, as did zinc, tin, iron and aluminum, in decreasing order of activity.

Vega (1950) found that granulation of ascorbic acid with anything containing even traces of moisture caused a large loss of activity both at the time of manufacture and during storage. Sodium metabisulphite and thiourea had little or no effect.

Sengupta and Gupta (1949), in a study of ascorbic acid injection, found that, whilst the major initial cause of destruction is due to oxidation and can be avoided by excluding oxygen and by the use of antoxidants, there is also a slow later auto-oxidation takes place which is not prevented by antoxidants but is retarded though not eliminated by rigid exclusion of oxygen. The Report on Stability of Pharmaceutical Preparations (1959) of the Danish Academy of Technical Sciences (D.A.T.S. Report) states that riboflavin and methylene blue have a sensitizing and photocatalytic effect on ascorbic acid when exposed to visible light.

Calciferol. This vitamin is particularly liable to oxidation and should also be protected from light. Vitamin A is also unstable in the presence of oxidizing agents. Oily solutions must be made from low peroxide oils containing an antoxidant such as 0.1 percent of hydroquinone. Campbell and McLeod (1955) reported that vitamin A is likely to decompose in multivitamin preparations, especially in liquid formulations. Vitamin E or tocopherol is also liable to oxidation but can itself act as an antoxidant.

General Incompatibilities of Vehicles and Excipients

Vehicles

Developments in the past few years have provided the pharmacist with many new vehicles and excipients

and these are being used for an ever-increasing range of medicaments, many of which are highly reactive substances. The possibilities of incompatibilities or unusual reactions are therefore enormous and we must therefore record and publish every example we can find.

Even with as simple a solvent as water difficulties may arise. Schou (1954) has shown that many samples of distilled water contain appreciable amounts of copper. Because of this the *Danish Pharmacopoeia* states that injection of adrenaline must be made with redistilled water.

The whole subject of "Water for Pharmaceutical Purposes" was the subject of a symposium at the British Pharmaceutical Conference in 1956. Saunders (1954) showed that deionized water complies with the B.P. tests for distilled water if the resistance is greater than 1 megohm and the monograph for purified water now allows the use of water purified by ion exchange to be used for galenicals but not for injections. Provided this water is stored in non-metallic containers, it can have advantages for the preparation of solutions of drugs which have their activity reduced by traces of metallic ions. My work (Whittet 1956; 1959) has shown that the water from properly operated mixed bed column type and two bed plants is almost always pyrogen-free. It might be possible for the pharmacopeias to permit the use of purified water for small dose injections.

Lloyd (1949) reported the development of lead contamination of distilled water after twelve hours' storage in a stainless steel tank. Schou and Gredsted (1951) have examined the oxygen content of water used for the preparation of galenicals and have shown that even boiled and rapidly cooled water can contain appreciable quantities. They recommend special procedures for preparing injections especially liable to oxidation. Most pharmacopeias specify the use of freshly boiled and cooled water for the preparation of solutions of drugs liable to be affected by carbon dioxide. It is interesting to note that freshly prepared deionized water is free from carbon dioxide.

Fixed oils and ethyl oleate, used as solvents for vitamins and other oil-soluble substances, must be as free as possible from rancidity and peroxides which may damage many medicaments. Hizon and Huyck (1956) pointed out that to ensure a reasonable shelf life for sterilized preparations of fixed oils for injection the addition of a suitable antoxidant is essential. Ramamurti and Bannerjee (1948) recommended that the free fatty acid content of fixed oils to be used as vitamin solvents should be less than 1 percent. Pernarowski and Chatten (1955) found that the stability of ephedrine in compound spray was influenced by the peroxides and anhydrides in oils.

Coloring Agents

Numerous dyes are used as coloring matters in medicines and the public health and other authorities of several countries have classified them into various categories according to their safety for use in foods and drugs. (In Great Britain the Food Standards Committee. In the U.S.A., the Coal Tar Dyes Regulations.)

In 1952 a sub-committee of the *British Pharmaceutical Codex,* of which I was chairman, reported on the suitability of many dyes for coloring noninjectable fluids and gave several examples of incompatibilities. (Codex Revision Committee 1952.) In 1956 the Pharmaceutical Society Laboratory Report showed that several dyes are liable to fade in the presence of 0.02 percent of sodium metabisulphite, especially in alkaline solution.

Lachman *et al.* (1958) studied the interaction between several certified dyes and quarternary ammonium compounds.

Preservatives

A large range of bacteriostatic drugs is available for the preservation of many types of medicaments. Incompatibilities for chlorocresol have been listed by Hadgraft and Short (1947, 1947a), McEwan and MacMorran (1947), Reeds (1947), Gilbert (1947) and Davis (1948). McEwan and MacMorran (1947) and Hind and Szekeley (1953) gave a list of incompatibilities for phenylmercuric nitrate.

Martindale (1958) gives a list of incompatibilities for phenol. Macek and Feller (1952) stated that some samples of liquefied phenol are incompatible with cyanocobalamin.

Benzalkonium chloride was recommended for the preservation of eye drops by Hind and Szekeley (1953) and by Lawrence (1955, 1955a). Both give lists of incompatibilities and the last paper evaluates the effectiveness of the compound in various ophthalmic solutions. Scigliano (1954) reports that benzalkonium is irritating to the conjunctiva in strengths greater than 1 in 3000.

Chlorobutanol has also been widely used as a preservative, but Murphy and Stoklosa (1952) and Gershenfeld (1952) have shown that appreciable decomposition of this compound takes place on sterilization. The *p*H of a 0.5 percent solution of chlorobutanol fell from about 5.5 to 2.8 and after sterilization the solution gave a reaction with silver nitrate. This was confirmed by Given and Laurie (1957) and by Gladhart *et al.* (1954). The latter also investigated the stability of several other bacteriostatics and found the most stable and useful to be benzethonium and chlorocresol. They reported some incompatibilities for benzethonium.

Thiomersal is another commonly used preservative

but Fujita and Vazakas (1958) reported that, on storing for a long time, solutions of this compound often undergo decomposition with the formation of a precipitate. This has been shown to be due to reaction of alkaline thiomersal with heavy metals from the glass containers. It can be overcome by using a mixture of sodium and potassium tartrate and citric acid as a chelating agent. Thiomersal is incompatible with heavy metals. Trisodium hydrogen edetate was not effective, giving a precipitate, possibly due to the formation of an insoluble iron edetate.

The para-hydroxybenzoate derivatives, such as methyl and propyl paraben, are widely used as preservatives. Van Abbe (1959) reported them as incompatible with non-ionic emulsifiers and Patel and Kostenbauder (1958) and Miyawaki *et al.* (1959) and Pisano and Kostenbauder (1959) showed that they react with sorbitan derivatives such as polysorbate 80. Goldstein and Ryan (1952), Williamson (1957) and Engelund (1956) give extensive lists of incompatibilities for preservatives.

The salts of ethylenediamine tetracetic acid (edetates) are now being extensively employed as chelating agents to prevent the effects of metallic ions on medicaments. Few incompatibilities have been reported. Morch (1958) found that the disodium salt was not effective in preventing discoloration of physostigmine and that 0.05 percent, the highest concentration used, increased the discoloration. Somers and I (Somers and Whittet 1958) found an incompatibility between the antimonyl tartrates and the disodium salt. An extensive test on compatibility of this salt is at present being carried out in my department and, so far, very few incompatibilities have been found.

Antoxidants

Among the most popular antoxidants for liquid preparations are sodium sulfite, sodium or potassium metabisulfite and sodium formaldehyde sulfoxylate. The title sodium bisulfite is used in the Spanish and United States pharmacopeias, but Martindale (1958) states that there is evidence that the true bisulphite does not exist as a solid and that what is often described as the bisulfite is actually the metabisulfite.

As I pointed out at the Rome Congress (Whittet 1951), metabisulfites undergo considerable decomposition in air, especially on heating in solution. Baly and Bailey (1922) and Phillips (1928) found very appreciable decomposition within a few days when solutions of potassium metabisulfite were stored at room temperature in incompletely filled bottles. Solutions in full bottles remained stable for at least 25 days. Mason and Walsh (1928), studying the oxidation of sulfites by air, stated that metabisulfites are unstable at 60 and 90°C. Schou and Rhodes (1951) showed that appreciable change of *p*H occurs in solutions of sodium metabisulfite on autoclaving. Gundersen and Morch (1955) found a loss of 50 percent in ampuls and almost 100 percent in rubber-capped bottles. They stated that their results with ampuls were very variable. G. E. Foster and I made similar tests in 1951 with similar results but we did not publish our results as they were so variable.

Bamann *et al.* (1958) found that sodium metabisulfite could cause deterioration of drugs such as adrenaline, morphine, p-hydroxyephedrine, and procaine by a process of hydroxylation.

Ward (1955) recommended the substitution of sodium sulfite for metabisulfite in physostigmine eye drops since the oxidation of the former causes a decrease in *p*H which promotes turbidity when physostigmine is added to old stock solutions.

The D.A.T.S. Report (1959) states that, although sodium metabisulfite prevents darkening of solutions of sodium aminosalicylate, it decreases the *p*H and increases the degree of decomposition.

The comparative instability of sodium metabisulfite towards oxidation is, of course, responsible for its protective action, since it is preferentially oxidized, but it seems that an appreciable portion may be lost during sterilization before it has time to exert its antoxidant effect. It is probably advisable, therefore, to replace the air with nitrogen in ampuls containing oxidizable substances even in the presence of metabisulfite. Whenever possible, ampuls should replace rubber-capped bottles for such solutions. Since sodium sulfite appears to be rather more stable than the metabisulfite and is an efficient antoxidant, it may be preferable to use the sulfite for pharmaceutical preparations.

Sodium formaldehyde sulfoxylate is also used as an antoxidant, but its stability towards sterilization is doubtful. The *Merck Index* (1952) states that the solid melts at 65°C. and decomposes at a higher temperature. Hardie *et al.* (1954) showed that this substance reacts with procaine hydrochloride giving a condensation product without local analgesic activity.

The alkyl gallates are used as antoxidants in fats and oils and to prevent peroxide formation in ethers, paraldehyde and related substances. They are incompatible with metals, ephedrine and many alkaloids. Janecke and Senft (1957) studied the compatibility of antoxidants with wool fat.

Suspending, Thickening and Emulsifying Agents

The incompatibilities of the older gums, such as acacia and tragacanth, are too well known to need repeating here, but some unusual reactions may be encountered. For example, the enzymes in acacia may cause thinning of emulsions (G. R. Wilkinson, Personal communication, D.A.T.S. Report 1959). Taub *et al.* (1958) showed that tragacanth can inactivate

some preservatives. Schwarz *et al.* (1958) found the stability and viscosity of tragacanth to be greatly affected by *p*H.

Higuchi and his collaborators have examined the possibility of complex formation between various drugs and excipients, *e.g.* polyesters and barbiturates (Higuchi and Lach 1954); polyethylene glycols and iodine (Guttman and Higuchi 1955); polyethylene glycols and phenolic compounds (Guttman and Higuchi 1956); cationic drugs and polyelectrolytes (Kennon and Higuchi 1956); and polyvidone and various substances (Higuchi and Kuramoto 1954, 1954a). Schwarz and Levy (1957) have examined the compatibility of Carbopol 394 with a wide range of preservatives.

Incompatibilities of the cellulose derivatives have been listed by Swallow and Whittet (1942) and Tillman and Kuramoto (1957). Nixon (1951) has reported that cellulose derivatives used in creams can cause skin irritation.

Martindale (1958) gives a list of incompatibilities for sodium alginate and Bollinger and Munzel discuss the effect of various substances on the viscosity of alginates. (1958) Wilkinson (Personal communication) has found that traces of iron reduce the viscosity of alginate gels.

Lesshafft and Dekay (1954) give incompatibilities for an extensive list of suspending agents.

The macrogols (polyethylene glycols) are used as excipients for ointments and injections. Incompatibilities are listed by Neuwald and Adam (1954) and Marcus *et al.* (1956). Those of the macrogol esters are given by Hadgraft (1954) and Johnson and Thomas (1955). Richards and I (Richards and Whittet 1955) studied the suitability of the sorbitan derivatives (Spans and Tweens) for various pharmaceutical purposes. The possible effect of these substances and of other surface active-agents as co-carcinogens has been the subject of reports by Setala (1956) and Riska (1956). Harris (1956), however, gave reassuring information on the relative safety of those in the quantities likely to be used in pharmaceutical preparations.

Aoki *et al.* (1957) have found that the non-ionic surface active agents may reduce the effects of several fungicides. Bolle and Mirimanoff (1950) reported antagonism between non-ionic detergents and antiseptics. Fishburn (1947) pointed out that sodium lauryl sulfate is incompatible with cationic drugs and that the reaction is not always a visible one.

Carless and Nixon (1957) have shown that oils in a very finely emusified state, as with modern emusifying agents, are more susceptible to oxidation than when in coarser emulsions or in the unemulsified state. Wilkinson (Personal communication) has told me that there appears to be an optimum water content of fats for avoidance of rancidity, deterioration taking place in the absence of water or in the presence of more than a certain percentage. Bean and Berry (1948, 1950, 1951, 1953) and Berry and Briggs (1956) have shown that the type of soap used for emulsifying phenolic disinfectants profoundly affects their bactericidal effects. Wilkinson (Personal communication) has found that the addition of the water softening substance, sodium hexametaphosphate, to Lysol splits the emulsion with separation of the cresols.

Buffers and pH Adjustment

The importance of maintaining the optimum *p*H for stability of many drugs and the use of buffers for this purpose is well recognized. The optimum *p*H for stability, however, may not be the optimum for pharmacological activity. For example, several of the local analgesics are more stable at a distinctly acid *p*H but for maximum activity they should be neutral or slightly alkaline (Bullock 1938).

Morch (1953), in a study of the stability of cinchocaine, showed that the optimum *p*H for stability is about 5, greater hydrolysis taking place at values below this and precipitation of base on the alkaline side.

In my experiments on the stability of cinchocaine and amethocaine loss of activity and increase of *p*H occurred together (Whittet 1954).

Bhatia and Barber (1955) found that the *p*H value had a profound effect on the analgesic effect of ethyl aminobenzoate in various ointment bases.

The D.A.T.S. Report (1959) quotes several examples in which adjustment of *p*H to the optimum value by means of hydrochloric acid gives more stable products than when buffers are used. Examples include atropine, hyoscine and cinchocaine.

The effect of *p*H on pain was studied by Lupton (1942).

In my study of sulfacetamide eye drops, 'blind' trials showed that more subjects complained of stinging with borate buffered drops than with unbuffered drops (Whittet 1949). Fenton (1951) showed that the eye can tolerate a considerable variation of *p*H without pain being experienced if the solution is isotonic. Scigliano and Skolaut (1954) found that buffered eye drops of atropine and physostigmine support bacterial growth more readily than unbuffered ones.

The important effect of buffering agents on the solubility of insulin is illustrated in Hallas-Moeller's (1952) brilliant research on the insulin zinc suspensions.

Flavoring Agents

Unexpected effects sometimes occur when unstable flavoring agents are used for oral preparations. For example, Eastland (1951) reported that quinine becomes even more obnoxious in the presence of certain flavoring agents. David and Huyck (1958) investigated the stability of potassium iodide in the presence of

various flavoring agents and Wesley (1957) has reviewed the whole subject of pharmaceutical flavors.

Perfumes

The use of perfumes in pharmaceutical products is discussed by Whiffin (1958) and by Morrish (1957). The former reported that some perfumes can cause discoloration of products and others, such as hydroxycitronellal, can react with stearate creams to produce a disagreeable odor. Perfumes containing a high percentage of aldehydes fade when included in ointments or creams. The latter stated that traces of bleaching agents left in fats and oils may cause perfumes to fade and that the development of unpleasant odors on storage of some perfumed products may be prevented by the use of antoxidants.

Unusual Effect with Various Forms of Medicaments

Tablets and Capsules

Little attention has been paid to the diluents used for tablets and capsules; substances such as lactose, sucrose, dextrose, and calcium phosphate merely being regarded as inert fillers. Evidence is accumulating, however, that, apart from actual incompatibilities, the filler may have a profound effect on the absorption as well as the stability of medicaments.

Dearborn *et al.* (1957) showed in animals that calcium phosphate markedly lowers the blood level obtained with the tetracyclines and Sweeney *et al.* (1957) confirmed this and also a similar effect with magnesium salts in human beings. Welsh *et al.* (1957, 1958) found that all the commerical samples of capsules of these drugs they examined contained calcium lactate as a filler.

My colleagues and I (Dent, Trotter and Whittet 1953) found that commercially available high potency tablets of calciferol contained calcium phosphate and that this can give rise to calciferol toxicity in patients treated with high dosage of such tablets.

In 1955 I reported that the use of sugars, especially monosaccharides, as diluents for aminophylline caused a marked discoloration of tablets (Whittet 1955). Stephenson and Humphrey-Jones (1951) found that cocoa causes increased loss of glyceryl trinitrate in tablets and recommended the replacement of the chocolate base with one containing glycerin and lactose. Price *et al.* (1957) reported that lactose inhibits the action of neomycin and polymyxin.

Ribiero *et al.* (1955) found that stearate caused decomposition of aspirin in A.P.C. tablets. Wilkinson has told me that he has evidence of the formation of stearic acid when magnesium stearate is used as a lubricant for tablets containing aspirin. Metallic ions such as Cu and Fe cause discoloration of aminophylline (Whittet 1955).

Bandelin and Malesh (1958) reported that magnesium trisilicate, sodium bicarbonate, and dibasic sodium phosphate cause very rapid decomposition of aspirin.

Another vitally important matter in the formulation of tablets is to ensure that the excipients used do not interfere with either the disintegration or the absorption of the medicaments.

Sperandio *et al.* (1948) pointed out that the efficiency of a tablet is to a great extent influenced by the speed with which it disintegrates. They stressed the importance of distinguishing between disintegration, the mere breaking up into particles or granules, and solution. Parrott *et al.* (1955), in their investigation into drug release from solids, emphasized the point still further. They state, "While the disintegration time of a tablet does influence the rate of drug release to the body, a more important aspect is the rate of release from the primary drug particle since solution of the drug is essential in order for absorption to take place. This, the release of a drug from the primary particle and its subsequent availability to the body is governed by the dissolution rate of the particles."

Evidence is accumulating that both the initial particle size of the drug and the type of binding agent used may affect its absorption.

Munzel (1954) showed that, unless specially treated, granules of lipophilic substances such as phenacetin do not disintegrate in water at 37°C. Griffin and Huyck (1955) showed that sodium bicarbonate tablets took longer to disintegrate when granulated with methylcellulose or alginic acid than wth starch mucilage.

Fishburn (Personal communication—results to be published) has told me that the particle size of phenindione makes a very significant difference to the absorption time. This is detectable both by measuring the drug content of the plasma and even more by the prothrombin time. This probably explains variations in potency which have been reported and previously ascribed to variations in tablet hardness. (Weiner *et al.* 1954.)

Torning *et al.* (1958) found that particle size influenced the absorption of "Tebamin" (the phenyl ester of para-aminosalicylic acid).

Particle size may also be important in the absorption of corticosteroids. Adamson (Personal communication) has told me that he has found this to be the case with prednisone. Obviously much research remains to be done in this field.

Another factor which can result in failure of absorption of medicaments in tablets is the application of an enteric coating which does not disintegrate. We have found intact tablets of potassium and of ammonium chloride in the stools of patients. Grainger (Personal communication) has told me that he has evidence from x-ray photographs of tablets passing through the intestinal tract unchanged.

Injections

Many factors influence the stability of injections. Some of these have already been mentioned and a few unusual reactions will now be discussed.

As simple an excipient as dextrose may cause several unexpected effects. Patton and Hill (1948) found that l-tryptophan, l-lysine and dl-methionine, and members of the B complex vitamins are destroyed on heating with dextrose. This may be of importance in intravenous nutrient solutions.

Griffin and Marie (1958) showed that dextrose decomposes on autoclaving in the presence of sodium lactate. Increasing concentrations of lactate and increasing *p*H increase the amount of decomposition.

It is well known that dextrose caramelizes on heating, especially in alkaline solution. We have found that this can be prevented by metabisulfite (Whittet 1954a). My colleagues and I (Bolton-Carter, Milne and Whittet 1952) showed that there was no difference in the incidence of thrombosis following the infusion of discolored buffered solutions and similar solutions in which discoloration was prevented by metabisulfite.

Several workers have shown that procaine reacts with dextrose forming a glycoside which is inactive as an analgesic (Cannell 1951, Ikeda 1957). This type of reaction may occur with other compounds containing a primary amino group. We have found that sodium para-aminohippurate reacts with dextrose to form a compound which gives false results in renal clearance tests. Dextrose is sometimes used to adjust the baricity of spinal analgesic injection. Obviously it should not be used for drugs containing a primary amino group.

Much attention has been paid to decomposition of adrenaline in procaine-adrenaline injections, but Briggs and Callow (1941) and Uri and Adler (1950) have shown that discoloration of plain procaine solutions occurs. This appears to be due to oxidation and is accelerated by traces of metals, especially iron, copper, silver, cobalt and cadmium ions.

Another simple substance which may cause trouble is sodium chloride. This may cause precipitation of colloidal dyes. Somers and I (Somers and Whittet 1956) found that it causes precipitation of Congo red with a marked increase in toxicity.

Some substances used as stabilizers may occasionally have unexpected effects. Chakravarty and Jones (1957) showed that d-saccharate and edetic acid used as stabilizers for calcium gluconate may actually accelerate precipitate formation.

Kokoski (1958), in a study of the stability of sodium aminosalicylate, found that sealing of solutions with carbon dioxide under pressure increased the rate of decomposition instead of reversing the reaction. Sodium metabisulfite and sodium formaldehyde sulfoxylate prevented the darkening but accelerated the rate of reaction. Buffering solutions to a more alkaline *p*H with sodium acid phosphate increased both the rate of darkening and decarboxylation and this effect was not prevented by antoxidants.

Replacement of the air in ampuls by nitrogen reduced darkening but not decarboxylation.

Shu-yuan and Wiese (1958) found that gases such as nitrogen, carbon dioxide and sulfur dioxide which have been used as stabilizing agents for menaphthone sodium bisulfite actually accelerate its decomposition.

Various solvents may be used to increase the stability of drugs. For example, propylene glycol is used for sodium phenobarbitone. I have found that some samples of this solvent give a precipitate with sodium phenobarbitone (Whittet 1955a).

A solution of local analgesics in propylene and polyethylene glycols gave rise to permanent nerve damage (Clarke *et al.* 1955) (Parsonage *et al.* 1955).

Both beeswax and aluminum stearate have been used to increase the viscosity and prolong the action of oily injections. Wilkinson informs me that when aluminum stearate is added to a mixture of beeswax and vegetable oil its viscosity is decreased.

Sargent (1957) showed that phenylmercuric nitrate and the para-hydroxybenzoate are incompatible with procaine penicillin and that, although phenol and benzyl alcohol are chemically compatible, they adversely affect the physical properties of suspensions.

Suppositories

The type of base used for suppositories can significantly affect the absorption of medicaments. Cacchilo and Hassler (1954) found that, whereas there was no difference between the amount of aspirin absorbed after oral administration and after suppositories with polyethylene glycol bases, there was significant difference when cocoa butter or glycogelatine bases were used. Peterson and Guida (1953) found a marked reduction in the release of aminophylline from cocoa butter based suppositories stored for one year. Riegelman and Crowell (1958), in one of their series of papers on the kinetics of rectal absorption, found that surface active agents and polyoxethylene polymers delayed absorption and that the relative particle size of drugs influenced their absorption rate.

Gross and Becker (1953) studied the release of drugs from various suppository bases and also listed some incompatibilities.

Ointments

The bases used for ointments can influence the effect of medicaments by incompatibility or by interfering with absorption. Varma *et al.* (1955 and 1955a) studied both the effect of various bases on absorption

and the incompatibility with numerous drugs. Wood and Rising (1953) examined the effect of emulsifying agents on antiseptic activity in dermatological preparations. Traub *et al.* (1954) found considerable variation in the activity of chlorine-liberating compounds in various bases.

Meyers *et al.* (1949) examined the effect of various bases on the absorption of phenol red and found that cetyl alcohol and silica reduced absorption from paraffin and wool fat bases.

Incompatibilities in the formulation of ointments have been reported by Hadgraft (1947), for hydrous ointment and (1954) for the macrogols. Plein and Plein (1953) studied the compatibility of silicone oils with 42 waxes and wax-like substances.

Calamine Lotion

The formula of this popular lotion has undergone many changes in recent years. King and Becker (1953) report that calcium hydroxide solution hastens sedimentation from this lotion regardless of particle size or suspending agent. Kok and Hopponeu (1949) studied the effect of many electrolytes on its stability. Wilkinson (Personal communication) has found that the addition of silica to calamine results in the liberation of carbon dioxide.

Ophthalmic Preparations

Reports of *Ps. aeruginosa* infections from contaminated eye drops in both Great Britain (Bignell 1951) and the U.S.A. (McCullough 1943) have emphasized the need for sterility in ophthalmic preparations. Many preservatives have been tested for use in eye drops. These have been reviewed by Engelund (1956). Incompatibilities for a wide range of ophthalmic drugs with preservatives have been given by Klein *et al.* (1954), MacPherson and Wood (1949), and Goldstein and Ryan (1952). Brewer *et al.* (1953) recommended the use of phenylethyl alcohol for ophthalmic solutions and studied its compatibility with several drugs.

Kral (1958) has made an extensive study of the stability of adrenaline in eye drops and its compatibility with other ophthalmic drugs. Laessoe (1958) found that resorcinol eye drops undergo oxidation which is accelerated by copper ions and retarded by metabisulfite.

Containers

Containers and closures were the subject of a symposium at the British Pharmaceutical Conference in 1953 and recent advances in the packaging of pharmaceutical products were discussed by Anderson (1959). The materials used for containers and closures include glass, metals, plastics, and rubber.

Glass Containers

Glass for pharmaceutical purposes has been comprehensively reviewed by Dimbleby (1953) who gives the approximate chemical composition of various types of glass containers used for a wide variety of pharmaceutical preparations. Her review also contains a valuable list of references and a short bibliography.

It has been known for many years that some types of glass can yield alkali to solutions with consequent deterioration of medicaments. The British and many other pharmacopeias stipulate the use of glass with a limit of alkalinity for any substance liable to decomposition through increase of alkalinity. The growing list of medicaments which must have the *p*H adjusted to an optimum value emphasizes the importance of this aspect.

It is also common knowledge among pharmacists that lead can be extracted from some glasses by certain medicaments and bottles of lead-free glass are usually directed to be used for solution of ammonium acetate, caustic alkalis and similar substances. Dimbleby (1953) pointed out that cream of magnesia can extract appreciable quantities of arsenic from glass and stated that the use of arsenic-free glass is advisable for storing all alkaline reagents. Schou (1955) has shown that non-resistant glass may have a deposit of copper on its surface but this can be removed by routine cleaning. Subrahmanyam and Majeske (1957) showed that silicate can be released to alkaline solutions from glass. They also report that the use of chromates for cleaning may result in absorption of chromium ions with subsequent release to medicaments.

Carrero (1955; 1956) has studied the release of boron from "neutral" glass. He showed that substances containing 'diol' groups such as calcium gluconate and glycerol are capable of dissolving appreciable quantities of boron from glass. In the case of the former the released boron had a stabilizing effect, but, in view of the potential toxicity of boron compounds, the presence of these substances as contaminants of medicaments is undesirable.

In a study of the decomposition of ascorbic acid Fischer-Jensen (1955) found greater stability in quartz ampuls than in ordinary ampuls and attributed this to freedom from traces of metallic ions. Foye (1955) showed that sodium aminosalicylate forms chelates with metallic ions such as those of copper, iron, cobalt, manganese and chromium and this reduces the antituberculous action of the compound.

These reactions must be remembered in both the preparation and storage of such medicaments. Schou (1955) has shown that copper and other compounds can be released from the apparatus used in preparing and filling solutions of drugs.

The treatment of bottles with silicones is now extensively used. Brill and Gumilevskaya (1958) found

that this reduces the release of alkalinity but Berry (1953) quotes experiments made by P.J. Parr showing that it gives no protection from flaking.

Hughes (1958) stated that silicone-treated bottles are at present unsuitable for pharmaceutical products. They are, however, being used for several preparations.

The appearance of flakes in intravenous solutions sterilized in glass bottles is a serious problem which has been discussed by Dimbleby (1953), by Berry (1953) and by Subrahmanyam and Majeske (1957). It is particularly liable to occur with phosphates, citrates, and various alkaline solutions. Dimbleby found the flakes to contain 80 percent of silicon dioxide with calcium, magnesium or aluminum oxides according to the type of glass.

Subrahmanyan and Majeske (1957) also give analyses of flakes. They also showed that pretreatment with N/100 acid delayed flake formation. I have found the same effect with citric acid solution (1947). Davis (1953) found that autoclaving glass with a solution of sodium metabisulfite also delayed the appearance of flakes. The *in vitro* and *in vivo* effects of such particles have been studied by Brewer and Dunning (1947).

Glass is used to protect many substances from light. The effect of various types of glass on the transmision of rays of various wave length is discussed by Dimbleby (1953). Among the ions used for coloring 'actinic' glass are iron, manganese, cobalt, and chromium.

Carlsen (1957) has also studied the spectral distribution of light sensitivity of drugs and has pointed out that glass should be as transparent as possible whilst cutting off the rays of harmful wave-length to the medicament. This is important to allow inspection of the clarity of injections. Very often the action of light on drugs in causing discoloration is an acceleration of an oxidizing process and may be prevented by the exclusion of oxygen or the addition of antoxidants. Some sulfonamides, however, darken on exposure to light despite these precautions (Whittet 1950).

Metal Containers

Numerous examples of the deleterious effects of metals on medicaments have already been mentioned.

Copper

Schou has published an excellent series of reports on the effects of copper on many types of preparations (1955, 1955a, 1955b, 1956 and 1957). These papers are in Danish with English summaries. They are also summarized in English by Schou (1957a) and there are many references to them in the D.A.T.S. Report (1959) (also in English).

Iron

Iron containers cause discoloration of phenols and react with many substances. Even some types of stainless steel will react with many medicaments such as methyl salicylate, oxymel of squill and other preparations containing acetic acid, and ammonia and senega mixture. (Boardman, 1949.)

Aluminium

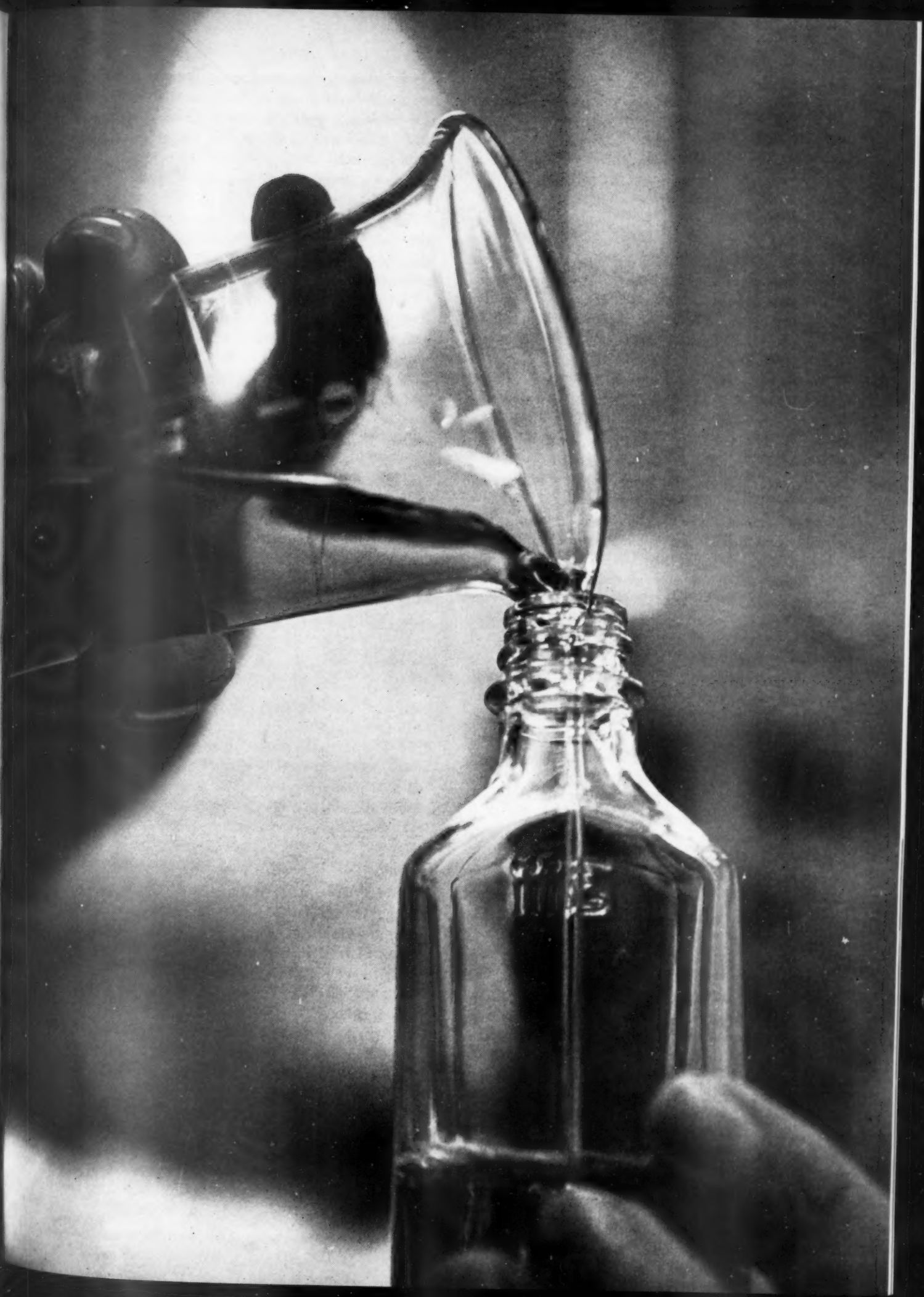
This metal is now widely used in containers for tablets and for collapsible tubes. The lubricant used during the extrusion process must be removed by a caustic wash otherwise it will cause blackening of tablets. Friction of tablets against the metal may cause scratching of the metal surface and discoloration of tablets. This can be prevented by applying a layer of vinyl or cellulose lacquer.

Aluminium containers are also used for aerosols, and Whiffin (1958) has reported that the metal can activate a number of reactions with perfumes, such as the formation of acetate from aldehydes and alcohols.

Aluminium tubes are now becoming popular as they are much cheaper than pure tin tubes. Boardman (1949) has reported that aluminium is not suitable for emulsion bases for the fatty alcohol emulsions reacted with aluminium tubes to form a white encrustation. Palmer (Personal communication) has told me that uncoated aluminium tubes are unsuitable for depilatories and for contraceptive jellies containing mercury compounds. The application of epoxy lacquer to the internal surface of aluminium tubes makes them much more resistant to attack. Such surfaces are very unreactive. Waxing, as well as the application of a lacquer, is used to protect aluminium tubes used for depilatories. For mildly alkaline substances, such as toothpastes, only a wax coating is necessary. Anodization of aluminium also has a protective effect. Stephenson (1953) stated that uncoated aluminum should not be used for materials outside of the *p*H range 6.5 to 8.0. Goettsch (1956) reported that phenylmercuric salts attack the aluminium caps of eye drop bottles.

Tin

Both pure tin and tin-coated lead are used for tubes. Tin is unreactive and seldom corrodes but is relatively expensive. It is said to be corroded by chlorides and by increase in acidity but Stephenson (1953) found that injection of morphine hydrochloride at *p*H 3.7 could be stored in tin tubes for several years without corrosion taking place. Because of the low melting point of tin and lead tubes epoxy resin coats cannot be applied. These tubes may be coated with vinyl or cellulose lacquers.



Lead

Because of its toxicity lead should not be used for tubes for preparations for internal use. Eastland (1951) reported an incompatibility of sodium alginate with lead tubes and Stephenson (1953) a reaction between silver picrate jelly and lead. The latter also stated that electrochemical reactions between tin and lead in the presence of an electrolyte often result in more contamination than would take place with a plain lead tube.

Plastics

Plastics in pharmacy formed the subject of a symposium at the British Pharmaceutical Conference in 1955, including papers by Child, Bull, and Fishburn. The types of container now made from plastics include tubes for semisolids, disposable enemas, disposable infusion fluid containers and 'giving sets,' eye drop bottles, and nasal spray bottles. Plastics are being used for screw caps and various types of closures.

Tubes are generally made from polyvinyl chloride or polythene. Plastic tubes are not completely impervious to water vapor and some loss, with concentration of aqueous products, is inevitable. This occurs to a greater extent with polyvinyl chloride than with polythene. Other volatile materials such as perfumes may also be lost.

Polythene tubes have the disadvantage of elastic recovery, hence they cannot be rolled up like flexible metal tubes. As a result of this, air is drawn into the tube with increase in the chance of drying out of the material and oxidation. Polythene also cannot be completely clear. It may be colored by the use of various pigments. On the other hand, it has the advantage of not needing any plasticizer.

Since no plasticizer is completely unextractable, their possible effect on the stability and toxicity of medicaments and foods is very important. The British Plastics Federation has published a report of a sub-committee on the toxicity of plasticizers. This report discusses the possible toxic hazards from the use of plastics as wrappers or containers for food. It suggests extraction tests and gives a method of determining a "Toxicity Quotient." Except when undesirable substances are known to be present, a material with toxicity quotient of less than 10 is considered to be safe for use with foods. The data for the common plasticizers, stabilizers, and other addenda are given.

Child (1955) gave the chemical properties of these and many other plastics and Bull (1955) discussed their use in containers and equipment. He mentioned the loss of water vapor through plastics, stating that it is particularly high with polystyrene and nylon. He also found an incompatibility between polystyrene and cellulose acetate used as parts of the same container and reminds pharmacists that the organic esters used as insect repellants attack plastics. Bull quotes Pinsky, Nielsen and Parliaman as having carried out a long term study of 67 chemicals in polythene bottles and having recorded data concerning permeability and physical effects.

The Plastics Division of Imperial Chemical Industries Ltd., has issued a booklet giving the compatibility of their polythene product "Alkathene" with many chemicals. The material is stated to be soluble in xylene, toluene, amyl acetate, trichlorethylene, paraffin and turpentine, all of which may be used in pharmacy.

Wsi-Ying Wu and Job (1954) used flexible polyethylene tubes of about 4 ml. capacity for eye drops. These have the disadvantage that they cannot be autoclaved. Plastics are now available which can be sterilized by autoclaving and might be useful for eye drops. The plastic would need to be fairly impervious to water vapor to prevent concentration of drops. J. W. Soulsby has told me that he has tested the storage of physostigmine drops in these containers and they seem as stable as in dark glass eye drop bottles.

Autian (1957) discussed the use of plastics for parenteral products. He gives rates of transmission of various substances through plastics and a list of incompatibilities.

Closures

The desirable properties of liners for metal and plastic caps have been discussed by Boardman (1949), Stephenson (1953), Bull (1955), and Fowler (1959, 1959a). It is well known that corks are attacked by many substances such as hypochlorites, permanganate, but a surprising contamination due to corks was that of cetrimide becoming infected with *Ps. pyocyanea* from the corks of stock bottles (Keen 1957).

Rubber Closures for Injection Solutions

Rubber closures for injection solutions have caused many problems and have been the subject of much research. Haworth (1953) and Berry (1953) have discussed the desirable properties of such caps. Both pointed out the difficulties of standardizing rubber for such caps and Berry quoted from his earlier work on the absorption of antiseptics such as chlorocresol from rubber. The mechanism of this absorption has been studied by Wing (1955, 1956 and 1956a), who has shown that both phenol and chlorocresol are absorbed until there is an equilibrium between the amount in the solution and in the caps. The amount absorbed is proportional to the concentration in contact with the rubber. Wing also discussed the effect of various rubber constituents on the extent of absorption. Royce and Sykes (1957) examined the absorption of a wider

range of bacteriostats and recommended that an equilibrium treatment should be worked out for each compound for the rubber to be used. They considered the phenylmercuric salts unsuitable to use in rubber-capped bottles. I can confirm this since I have found that phenylmercuric salts cause blackening of many rubber caps. (Whittet 1957). Weiner (1955) has reported that the pre-treatment of rubber caps with thiomersal did not prevent them from absorbing this compound from solutions. Bellamy and Watt (1949) found that some types of rubber inactivate penicillin.

Berry (1941) reported that rubber caps can react with metabisulfite and my colleagues and I showed that pre-treatment with sodium metabisulfite can reduce the loss from solutions (Whittet 1946; West and Whittet 1948; Foster, McDonald and Whittet 1950).

Metabisulfite was found by Milosovich and Mattocks (1956) to increase the absorption of water by rubbers. The same workers (1957; 1957a) studied the effect of vapor pressure, bisulfite, washing, and organic substances on absorption of water by rubber. Blaug *et al.* (1958a) studied moisture transmission through closures.

Rezner (1953) found that rubber caps may release zinc to a sufficient extent to be physiologically objectionable or to cause insoluble particle formation by interaction with other constituents of the solution or with the container. Fowler (1959) has discussed the treatment of rubber caps to minimize contamination of injections with particles.

Rubber is incompatible with nikethamide (Berry 1953) and paraldehyde (Marston and Allchin 1952).

Plastic Closures

Nielsen (1958) compared closures made from polyvinyl chloride with rubber caps in an extensive series of tests including physical properties, extraction of material by water, by solutions of drugs and the effect of the caps on absorbing substances from solution. He concluded that polyvinyl chloride caps were superior to rubber from the first three points of view but that they did not seem better than rubber in the fourth respect.

Testing of Containers

Many tests have been suggested for testing the suitability of containers for the storage of pharmaceutical preparations, but, undoubtedly, the best test is to examine products after storage in the containers for prolonged periods. For this reason the American Pharmaceutical Association Report on the Stability of Drugs at Various Temperatures (1944) is most interesting and useful. This gives an account of the examination of an extensive list of army supplies stored under various conditions over periods of several years.

Stephenson (1953) devoted most of his symposium paper to the testing of containers and closures for pharmaceutical products and Fowler (1959, 1959a) listed the essential properties of good packaging and gives a method of estimating shelf life together with tests for the mechanical strength of packages.

The *British Pharmacopoeia* contains a test for limit of alkalinity of glass and the *United States Pharmacopeia* tests for chemical resistance to water and acid at 121°C. and for light transmission. The former gives criteria for containers for injections and the latter for containers in general.

Turner *et al.* (1923) utilized the reaction involving the precipitation of alkaloids from their salts by alkalis as a qualitative test of the durability of medicine bottles.

Stephenson (1953) suggested the following tests for efficacy of containers: (1) Test for inertness to product —on storage at normal low and elevated temperatures "the container shall not interact physically or chemically with the drug which it holds so as to alter the strength, quality or purity of the drug beyond the official requirements" (U.S.P. requirement). With dry solids inspection of the drug and the inside surface of the container will generally suffice. With liquids changes in color, clarity, or *p*H may be found. The surface of the container should also be examined. Assay of the product may be necessary. (2) Strength of container—by handling or a simple drop test. (3) Tests for leakage. Containers are stored at elevated temperature in various positions and are weighed and examined periodically. (4) Permeability Tests. In the case of volatile substances storage at elevated temperatures with periodic weighing will suffice. For moisture permeability storage under controlled humidity conditions with temperature fluctuations and repeated weighings is usually satisfactory.

Testing of Closures

Several attempts have been made to standardize rubber caps. The World Health Organization set up a subcommittee of Dr. L. C. Miller, Professor E. Selles, and myself to investigate the problem in collaboration with interested organizations in each country. The British Standards Institution has recently circulated a draft standard for rubber closures for parenteral products. It suggests standards for workmanship and finish and for uniformity of color. Tests are given for penetrability, fragmentation, self-sealability, water extract, and alkalinity or acidity and standards are suggested for these properties. A further appendix gives proposed method for testing compatibility of the closures with medicaments. This is by storing under various conditions and examining at intervals both the solution and the closures. Physical and, if necessary, chemical and biological tests should be undertaken.

Penetrability is tested by the weight necessary to cause penetration under specified conditions and fragmentation by the number of particles found in solutions after the cap has been pierced a specified number of times.

Permeability to water vapor is measured by placing calcium chloride in bottles sealed by the caps, storing them under conditions of high humidity, and examining them for increase in weight.

Self-sealability may be tested by forcing air into an inverted bottle containing water and noting if any leakage occurs through the closure, or by placing methylene blue in containers sealed with the caps immersed in water and applying a vacuum. No sign of leakage should occur. For this test a specified number of punctures is made in each cap.

Determination of water extract is made by refluxing a specified number of caps in distilled water for a specified time, evaporating the water to dryness, and weighing the residue. Acidity or alkalinity is measured by autoclaving the caps with water at *p*H 6.8 to 7.2 and titrating with acid or alkali, using bromothymol blue as indicator.

Stephenson (1953) outlined in detail a closure efficiency test applicable to containers sealed with all types of closures. The containers are half-filled with a suitable desiccant (freshly dehydrated magnesium perchlorate or anhydrous fused calcium chloride previously heated to 150°C. for 3 hours). They are then placed in an atmosphere of about 90 percent humidity and subjected to temperature fluctuations over a prolonged period. The containers are weighed at intervals and the efficiency is expressed as a percentage calculated as follows:

$$\frac{\text{Mean gain in weight of control}}{\text{Mean gain in weight of test}} \times 100$$

Stephenson gives a table of the results of the application of this test to several types of closures.

Christiansen (1952) made a thorough examination of the effect of rubber on distilled water and made the following recommendations for rubber for pharmaceutical purposes.

Vulcanized rubber should not be colored. After autoclaving with water it should not give a precipitate or more than a slight yellow color with Nessler's reagent.

The solution obtained after autoclaving a specified number of caps with distilled water on evaporation should not give a weight greater than a specified amount.

Christiansen also specified limits of *p*H change and electrical conductivity of distilled water autoclaved with caps. He outlined a test involving a reaction with dithizone (diphenyl thiocarbazone) which he claimed would give an indication of freedom from pyrogenetic activity.

Morrisey and Hartop (1957) suggested an extraction test for rubber closures involving autoclaving them at 121°C. for 30 minutes and examining the solution for turbidity (measured in nephalos units) for reducing agents and for *p*H charge. They propose limits for these factors and claim that the method is applicable for a preliminary evaluation of new materials and for routine control of established materials.

A modification of this test was accepted by the U.S.P. Open Conference on Closures for Parenteral Solutions (1958) and manufacturers were asked to submit the results of a collaborative study of two types of closures by this method. The results were submitted as a report to the Pharmaceutical Manufacturers' Association in October 1958. The figures from 14 different laboratories showed significant differences between samples as measured by nephalos units, and in most cases by reducing substances; *p*H measurements showed little significant difference. The difference between laboratories carrying out these tests was, however, highly significant.

Hopkins (1958) has suggested a test for measuring particles from punctured rubber caps. The mechanism of production of these particles, known as 'coring' in the rubber trade, is also discussed and measures are suggested for reducing it.

It is obvious that much work remains to be done before adequate standards for rubber closures can be adopted and enforced.

Summary and Conclusions

The numerous totally unexpected reactions outlined in this paper emphasize the importance of a thorough testing of all new formulae from the points of view of stability, efficacy and toxicity. In addition, prolonged storage tests should be carried out under various conditions to guard against delayed reactions and to test the effects of containers and closures.

Since the free exchange of experiences in this field will improve the pharmaceutical services in all countries, pharmacists should be encouraged to publish their results. However small any individual example may seem, each has its importance in building up a complete knowledge of the properties of drugs, vehicles and excipients. International exchange of ideas is especially valuable and symposia of this kind can be the means of disseminating knowledge throughout the widest possible field.

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Group leaders for the clinic sessions hold an informal meeting at the Columbus Institute

1960 INSTITUTES
Columbus & Minneapolis

by PAUL F. PARKER

► BEGINNING WITH THE FIRST INSTITUTE on the campus of the University of Michigan, in 1946, hospital pharmacists have had the opportunity to participate regularly in dynamic continuing education programs. Perhaps more than any other single factor, the institutes have helped to raise the standards of hospital pharmacy practice and improve the qualifications of its practitioners. This is not enough. With the changing role of the hospital in modern medical care, and the ever increasing importance of drugs in diagnosis, treatment, and prevention of disease, we cannot afford to become stagnant or complacent. Even the pharmacist who has just completed special education and training in hospital pharmacy can soon fall behind unless he regularly and routinely follows some course of continuing education. Hospital pharmacy is on the move. As an organized professional specialty, we must continue to provide an up-to-date continuing education program. Our institutes must remain dynamic.

Students at the Minneapolis Institute hear Norman Hammelman from the Medical Area Office of the Veterans Administration in St. Louis discuss "Elements of Good Supervision"

We now have two general institutes each year, and for the first time a specialized institute is being held this month in Chicago. This specialized program will treat a single subject in depth for the particular benefit of hospital pharmacists who have been in practice for some time. Enrollment for each general institute

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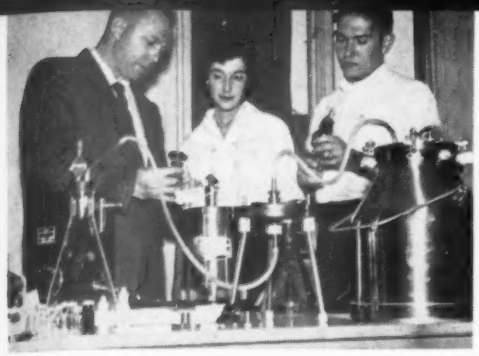

William Tester (left), Chief Pharmacist at the University of Iowa, answers questions for two students concerning equipment which he demonstrated at the Minneapolis Institute

is limited to 125 registrants. There are from 400 to 500 new pharmacists entering hospital pharmacy each year. The enrollment for the specialized institute is limited to 100 registrants, yet there are 4500 to 5000 pharmacists who regularly practice in hospitals. Therefore we may well ask, "Are we planning the institutes to fully meet our needs?"

The challenges of institutes are tremendous. To help meet these challenges, it may be appropriate to review our present procedures for planning and conducting institutes. By doing so we do not wish to imply that the present methods are best, or even good enough.

The institutes are conducted by the American Hospital Association in cooperation with the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS and the American Pharmaceutical Association. In addition, the local hospital pharmacy organization, the college of pharmacy, and the state hospital association serve as sponsors. Participation by this broad group of organizations serves to aid in planning and conducting the programs, but perhaps most important, stimulates attendance.

The hospital pharmacy institutes are only a fraction of the total number of such programs conducted by the A.H.A. The unusual feature of this arrangement is

Russell Lovell, Chief Pharmacist at the Akron City Hospital demonstrates equipment at the Columbus Institute with the assistance of Jeanette Sickafoose, Chief Pharmacist at the Aultman Hospital in Canton, Ohio

Sister Florentine from Columbus demonstrates equipment for the preparation of sterile products as Louis Jeffrey, Albany, New York looks on

Dean George Hager (center) of the University of Minnesota College of Pharmacy takes Joe Oddis (left) and Paul Parker on a tour of the campus

Hospital pharmacists met on the campus of the University of Minnesota in Minneapolis last August

that hospital pharmacists have worked very closely with the A.H.A. through the years in planning and conducting the hospital pharmacy institutes. This, we believe, has helped to improve the programs in spite of continuously increased costs. Hospital pharmacists are grateful to the A.H.A. for conducting these programs, sometimes at considerable expense, at a time when their own professional organization would not have had the facilities to conduct them. The fact that the A.H.A. has conducted the programs has probably also had some effect upon the attendance, because under this arrangement hospital administrators may have been more willing to send their employees.

Scheduling Facilities

Hospital pharmacy institutes do not "just happen." They required months of scheduling, planning, and arranging. With few exceptions, they have been held throughout the years on university or college campuses in order to achieve an academic environment. Such facilities are less expensive for the registrants. Since many universities and colleges have large numbers of professional groups using their facilities between semesters for continuing education programs, it has become necessary to schedule institutes as much as two and three years in advance.

The selection of a location for an institute probably has more to do with attendance than any other single factor; however in making a final decision, location cannot be placed above the need for adequate facilities. The institutes which have been held in the Mid-West have consistently had a larger registration than those located in either the East or the West. Ideally, it would be desirable to evenly distribute the locations between the East, West, North, South, and Mid-West. The majority of practicing hospital pharmacists should have the opportunity to attend an institute once every two or three years without being away from their department too long; there should not be undue expenses for travel, and the program should be adapted, to some extent, to the needs of the area. However, location cannot be placed above the need for adequate and suitable facilities.

The format for the institutes has become somewhat standardized, therefore the general requirements for facilities are fairly constant. A general meeting room is required which will accommodate 125 people seated at tables. This arrangement is most comfortable, and it is convenient to take notes. The acoustics in the room should be good; there should be some provision to darken the room in order to show slides, and there should be no posts which will obstruct the view to the stage or podium. There should be an elevated stage, either temporary or permanent, which is large enough to seat 8-10 people for group presentations. Good public address and visual aid equipment are essential. In addition, there should be 10 small conference rooms available for conducting the clinic session groups during the afternoon. Each room should accommodate at least 15 people. No special facilities are required for these rooms, since the clinic session meetings are informal.

Dormitory-type sleeping facilities are preferred and most registrants do not mind sharing a double room. The entire group may be housed in the same dormitory by assigning women to one wing or section and men to another. Facilities should be available to house 10-12 nuns in a separate section of the dormitory and the 10-15 faculty members are usually assigned single rooms.

Dining facilities may either be cafeteria or dining room style. It is preferable to have the group eat alone, rather than in a public dining area and the facilities should be located nearby the sleeping quarters and meeting rooms.

Program Planning

The programs for the institutes are developed initially by the ASHP Committee on Program and Public Relations. Since this Committee is composed of practicing hospital pharmacists, there is adequate opportunity to include topics which represent the interests and needs in actual practice. The Committee's recommendations are reviewed and approved from a broad viewpoint by the ASHP Executive Committee. The program is then developed in final form by representatives from the American Hospital Association and the Society. At this point particular attention is given to observations at previous institutes, and suggestions made by previous registrants, adaptability of the topics to various methods of presentation, availability of speakers, etc.

The program usually consists of from 25 to 35 different presentations. These are divided according to 5 or 6 principal themes, which indicate the broad emphasis of the program. The themes of the 1960 institutes are typical of each program and included: "Elements of Pharmaceutical Dispensing," "Maintaining Standards of Practice," "Improving Pharmacy Administration," "The Hospital Formulary System," and "Professional and Organizational Activities." By comparison with the program themes ten years ago, it may be noted that more emphasis is given to topics such as "service" and "the formulary system." Thus the programs do represent the current interest and needs of hospital pharmacists in actual practice.

Although the organizational arrangements for developing the program may seem involved, the procedural aspects of programming are even more detailed. These factors undoubtedly account for the high quality of the hospital pharmacy institute programs and, in turn, the excellent attendance record over a period of fifteen years.

The manner is which the program is presented is

of no less importance than the topics to be presented. The institute faculty members contribute their time and efforts without charge, thus it becomes the responsibility of the planning group to go as far as possible to assist the faculty. Primary consideration is given to the types of presentation in order to provide program diversification.

A comprehensive program outline is prepared which serves as a guide to members of the instructional staff and gives a summary of the total institute content. This outline contains a rather detailed description of each topic to be presented, thus giving the faculty member a clear understanding of his role in relation to the total institute program. This method aids in achieving consistency and uniformity in developing the various themes and prevents overlapping of subject matter.

The value of the total program can perhaps best be measured in terms of the specific ideas which the registrants gain that can be implemented in their departments. Faculty members are urged to provide mimeographed and printed materials concerning the topics they present. This usually does not include distribution of the complete presentation, but an outline or some specific information which cannot easily be copied in the student's notes.

The complete program is published in the ASHP JOURNAL with information concerning registration, housing, fees, etc. An application, which includes a brief program outline, is mailed to the administrator of every member hospital of the American Hospital Association. In addition, applications are sent to all members of the ASHP. Hospital pharmacy institutes have become so well known that publicity presents no particular problem. It is necessary to publicize information about the programs, but rarely necessary to promote attendance.

An institute program is more than a week-long series of presentations. Each registrant is encouraged to "live" hospital pharmacy from the time he arrives until he leaves. Thus, planning the institute is important, but coordinating the program to influence and direct the activities of the registrants throughout the week can well make the difference between success and failure.

Conducting the Institutes

The institute registrants arrive on Sunday afternoon, preceding the opening of the program on Monday morning. The first job is to get acquainted. The local hospital pharmacy group sponsors a reception beginning about four o'clock, which is usually held in the lounge of the dormitory headquarters. Hosts and hostesses are designated with appropriate name tags. Each enrollee is registered immediately upon arrival, given a name tag and a mimeographed list of all the registrants. These lists give each registrant's hospital, its size, and his position. Usually from 65 to 80 percent of the registrants have never previously attended an institute, therefore a majority of them have never met previously. Registrants are introduced in an informal environment and encouraged to get acquainted by discussing their favorite professional subject. Since enrollees and faculty arrive continuously throughout the afternoon and evening, it is a challenge to try to meet everyone and remember their names the following day. With some 125 registrants and 12 to 15 faculty members, getting acquainted must necessarily continue throughout the week, therefore everyone continues to wear the name tag.

Next comes the tasks of orienting the faculty and organizing the student body. One coordinator meets with the entire faculty beginning about 9:00 P.M. They are introduced to the chairman of the local committee and the dean of the school of pharmacy, briefed on the arrangements and facilities at the university, and given the opportunity to discuss the program, either in general, or regarding their own particular responsibility. Since faculty members take turns serving as presiding officers throughout the week, this meeting provides a good opportunity to discuss timing, question periods, etc. At this point, timing can be discussed in an impersonal manner and it is a most opportune time to do so. In fact, individuals who are to serve as presiding officers can be requested to interrupt speakers who do not follow the timing schedule.

Faculty members are also encouraged to spend a maximum amount of time with the registrants during meals and at times when the program is not in session. The faculty members meet as a group each day while the students attend their own group meeting.

The student body is organized into clinic session groups of appropriate size (usually 12 or 13 each), according to the bed capacity of the institution with which the student is associated. Each group is assigned a group leader, selected from the student body, who acts as a moderator during each session. The groups meet for a period of one hour in an appropriate size seminar room immediately following the program each day. Each group leader is charged with three responsibilities: (1) to have the group discuss ideas presented in terms of their application to the departments in which the students are employed, (2) to give each student the opportunity for individual expression, and (3) to evaluate the day's program. The moderator must encourage total participation in the group discussions. He serves as a recorder and is required to report to the institute coordinator daily after each clinic session. All members of the faculty are available to serve as resource advisors to the clinic session groups, but participate in the discussions only as they are invited to do so. At the end of the week, a clinic session is held on the stage before the entire institute body, in

which the group leaders and institute coordinators participate.

Group leaders are selected from the student body by the coordinators as they arrive on Sunday afternoon. Since there is so little time to estimate the qualifications of the students who are best qualified, the selection is made, for the most part, by guess. Several students serving hospital pharmacy internships have proven to be especially good group leaders; however, it is difficult to generalize on the preliminary qualifications for serving as group leaders. If the student agrees to do his best, he usually comes through with an excellent performance.

The clinic session leaders meet with the coordinators late Sunday evening to get acquainted, discuss the purposes of the clinic sessions, and receive instructions concerning methods for carrying out their assignment. The instructions consist of specific suggestions for having the group become well acquainted; methods of selecting a topic for discussion; suggested techniques for keeping on the subject which has been selected for discussion; ideas for getting each individual to participate in the discussion, or for working with individuals who tend to "control" the discussion; summarizing the discussion, etc. On Monday the group leaders have another meeting during the lunch period, when the coordinator demonstrates for the leaders by leading a discussion in much the same manner as they will be required to do when they meet with their own groups in the afternoon.

Each group leader then meets separately with the coordinator during the evening to evaluate their progress during the first clinic session meeting. This report provides the coordinator with the opportunity to detect weaknesses in the leader's methods and also obtain general impressions about the overall student body reaction to the program. These impressions are passed along to the faculty at their daily meetings. The group leaders and coordinators have lunch together each day to improve discussion group methods and provide an organized medium for faculty-student liaison.

When the program begins on Monday morning everyone is keyed with eager anticipation. The coordinator gives additional instructions and introduces the members of the faculty. The stage has been set for an intensified week of work and everyone now realizes that an institute begins at 8:30 each morning and lasts until the "bull-sessions" are ended in various parts of the dormitory. As might be expected, some of these informal sessions last until very late at night.

The presentations are interspersed with ten minute coffee breaks both in the morning and afternoon. Even these require some detailed planning in order to serve 125-150 cups of coffee in 5 minutes or so. The lunch period usually lasts 1½ hours.

When one considers the program schedule—8:30 to 12:00 and 1:30 to 5:00 daily with two evening sessions—it is immediately apparent that there must be a constant change of pace. This change is accomplished primarily by diversification in the types of presentations. For instance, a straightforward lecture may be followed by a demonstration, then a lecture with supporting visual aids, a panel discussion, etc. If possible, no more than one type presentation should be included within a single half-day period. Usually the evening sessions are completely audience participation type programs.

Even though there is only a rare opportunity for the institute registrant to go his own way, there is scheduled time for relaxation. The Monday night program at the Minneapolis Institute which was arranged by the local group, was typical. The students and faculty traveled by bus to an excellent restaurant located 25 to 30 miles from the campus. Each had a dutch-treat steak dinner and saw an excellent show. Even in this environment, hospital pharmacy was the principal topic of conversation on the busses and over the dinner tables. By this time there are no strangers and even though you may not remember everyone's name there's no problem in "talking shop."

The last day of the institute comes all too quickly and the program concludes with a series of summaries designed to help each registrant put into practice the ideas he picked up throughout the week. Over the past two years one presentation has been made under the title "Implementing Institute Information." It not only includes suggestions for applying worthwhile ideas, but also develops a stimulating philosophy about participation in continuing education programs.

Next, the group leaders review some of the most interesting topics which were discussed in their clinic session meetings. Several methods have been used for student group discussions during the fifteen year history of hospital pharmacy institutes. The value of these sessions is difficult to evaluate and perhaps it would be worthwhile to obtain the advice and opinion of an "expert" in group dynamics. I have been very interested in this aspect of the institute programs during the past four years and one observation seems noteworthy. This is the continued interest and leadership in hospital pharmacy which is shown by the people who serve as institute clinic session leaders. The factor may have some relation to the development of organizational leaders in hospital pharmacy.

Throughout the week one member of the faculty has written a brief summary statement concerning each presentation. These are compiled as an overall review and forwarded, along with a letter from the Secretary of the A.H.A. Council on Professional Practice, to each registrant's administrator. This further paves the way

for each registrant to implement the ideas which he may have picked up throughout the week.

Planning and conducting institutes is no small task. It requires seemingly endless hours of work both by staff and volunteers. When we begin to plan for expanding either the scope or the number of institutes, these factors must be considered.

The American Hospital Association, which has conducted the hospital pharmacy institutes for fifteen years, has a well balanced overall institute program. If the present institutes do not fully meet the needs of our speciality (and one should not infer that they do not), is it the A.H.A.'s responsibility to change, or is it the responsibility of our own ASHP? Perhaps it would be worthwhile to study the adequacy of the institutes as a continuing education program for our specialty.

What about the location of the institutes? Is it possible for a majority of our practitioners to attend these programs if they wish to do so, or their hospitals are willing to send them?

Do the programs serve the needs of a majority of the people who attend? The present procedure for program planning has been revised through the years. It may be based upon sound principles or the procedure may have evolved to meet the needs at the time. Should a program include the topics which registrants request, or should it include topics they should learn about? Should we reproduce and distribute all papers presented on the program? Should the program schedule be lighter or heavier?

Should the institutes be national or regional? Should they last three days or five days? Should the institutes continue to be held on college campuses, or would hotel or other public facilities be suitable?

The answers to these questions require careful deliberation. They may be considered analogous to an evaluation of the procedures and services in our own departments. First, we must determine the effects of a change in its total ramification. Next, do we have the facilities and personnel to effect a change? What will be the cost? How can a change be implemented? Finally, we should evaluate the effect of the change.

This review of hospital pharmacy institutes is in no way intended as a criticism of them. In fact, our institutes may well be envied by other professional organizations. However, we must be alert to keep them dynamic—by constant evaluation, evolution, and growth.

Pharmacy at A.H.A. Convention

► HOSPITAL PHARMACY was represented by ASHP leaders at the recent Convention of the American Hospital Association in San Francisco. Participating in one of the program sessions was Past President Vernon O. Trygstad and Secretary Joseph A. Oddis, along with A.H.A. representatives W. K. Hegarty, Bakersfield General Hospital, Bakersfield, California, and Alanson W. Willcox, General Counsel of the A.H.A.'s Washington Service Bureau. The subject for discussion in this session—the hospital formulary system in hospitals—drew much attention.

Approval of the "Guiding Principles in the Operation of the Hospital Formulary System" (See pages 601 through 612) by the ASHP at its Annual Meeting a few weeks earlier and by the A.H.A.'s House of Delegates at this Convention provided much for discussion. The Guiding Principles had been developed by the Joint Committee of the American Hospital Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS working over a period of several years. Endorsement by the two organizations constituted approval of the formulary system and its generic name concept as essential in providing rational drug therapy in hospitals.

In the panel discussion, members pointed out the reasons for the formulary system, distinguished between the "formulary" and the "formulary system" and considered the legal implications.

Other actions taken by the A.H.A. at the San Francisco meeting and reported in *Hospitals* include:

—A recommendation that a national approval program for hospital administration be developed because the "American hospital means too many different things to too many different groups to leave the evaluation to each interest the hospital serves" and to "have no alternative but to go in the direction dictated by the most vocal and strongest of the various interested forces."

—The completion of the major task involved in melding the two national Blue Cross organizations into one stronger group which, in partnership with the Association, can guarantee the survival of voluntary prepayment.

—The swift rejection by the House of Delegates of a proposal that the A.H.A. embrace the social security approach to the financing of the health care of the aged.

—Criticism of hospital financing as "still in the handicraft stage" and a proposal for a $20 million advertising solution of the program.

—The adoption of a guiding pricing policy for hospitals which urged hospitals in the same community to follow in establishing rates which should be as inclusive as is practicable yet ensure equity and understanding.

Therapeutic Trends

edited by WILLIAM JOHNSON

A New Sulfonamide

A new sulfonamide, Ro 4-2130 (5-methyl-3-sulfanilamido-isoxazole), has shown potent *in vitro* and *in vivo* activity against pneumococci, staphylococci, streptococci, coli bacteria and *Klebsiella pneumoniae*. Acute and chronic toxicity studies in laboratory animals showed this compound to be distinctly less toxic than several other sulfonamides in current usage. Brandman and Engelberg in *Current Therapeutic Research* 2:364 (Aug.) 1960 point out that an interesting feature of Ro 4-2130 is the high cerebrospinal fluid levels attained for up to 12 hours after administration. This is of potential clinical significance in infections of the cerebrospinal system. Therapeutic blood levels were reached within two hours and maintained up to the twelfth hour following administration of single two gram dose of Ro 4-2130 to four patients. In five patients on the multiple-dose schedule with a dose of three gram on the first day followed by two gram daily in two divided doses, a very satisfactory concentration in the blood was obtained from the 24th hour until the end of the experiment. The drug in the blood was largely in the free or antibacterially potent form, whereas it was excreted largely in the acetylated form. Compared with sulfadimethoxine, Ro 4-2130 produced lower peak blood levels at all three single-dose levels; however, with the four gram dose peak blood levels of both drugs were nearly equal. These studies indicate that Ro 4-2130 possesses the characteristics of a therapeutically effective sulfonamide and that clinical trials are warranted. Ro 4-2130 was supplied for this study through the courtesy of Hoffmann-La Roche Inc.

SYLVIA SCHMIDT

Diphenylthiocarbazone (Dithizone) In Carcinoma Of The Prostate

Use of diphenylthiocarbazone in the treatment of prostatic cancer in man was suggested by observation from animal experiments which clearly demonstrated that this zinc-chelating agent suppressed canine prostatic function in terms of prostatic fluid volume, zinc uptake, zinc concentration and the histological appearance of the prostate gland. Ten patients who had carcinoma of the prostate, with and without metastases, were treated with diphenylthiocarbazone (dithizone). Two patients with metastases died, one from renal failure, but improvement of urinary symptoms and reduction in size and consistency of the prostate were observed in most cases. Complete relief of pain due to osseous metastases was observed in all three patients. Body weight and appetite were maintained at normal levels or improved. Mei-Chiau Lo in *Canad. Med. Assoc. J.* 82:1203 (June) 1960 reports that no major toxic effect from diphenylthiocarbazone was observed. Histological evaluation of the prostate after use of diphenylthiocarbazone revealed a variable degree of degeneration and atrophy of neoplastic tissue. All surviving patients have been followed up in the outpatient department with no clinical evidence of recurrence noted seven months after treatment. Diphenylthiocarbazone (dithizone) employed for dithizone solution was obtained from the Fisher Scientific Company, Montreal.

SYLVIA SCHMIDT

New Analgesic For Patients With Neoplastic Disease

A new synthetic analgesic material, piminodine ethanesulfonate, ethyl-4-phenyl-1(3-(phenylamine) propyl) piperidine-4 carboxylate ethanesulfonate, was used in 28 patients with neoplastic disease. The dose was 50 mg. every 3-4 hours orally or 20 mg. every 3-4 hours subcutaneously. In 19 patients, pain was associated with skeletal metastases; in 4, retroperitoneal metastases; in 2, liver involvement; phantom pain following amputation was present in 2, and a granulating perineal wound in one. Results were good to excellent in 78.5 percent of the patients, fair in 14.6 percent, with a poor response in 7 percent. No adverse effects on the hemograms or evidence of renal or hepatic toxicity were noted. The ability to relieve pain without inducing excessive sedation of the patient and freedom from other untoward effects such as nausea, vomiting, and constipation were most helpful in the management of the group of patients. D. Molander, in *Current Therapeutic Research* 2:370 (Aug.) 1960, adds that in a small number of patients, the additional use of Trancopal, a tranquilaxant, seemed helpful and would appear to warrant further investigation. This product was supplied as Alvodine ethanesulfonate by Winthrop Laboratories.

SYLVIA SCHMIDT

THE LAW
of hospital pharmacy

edited by GEORGE F. ARCHAMBAULT

► *Because law is a complex specialty made so because of the existence of a set of Federal laws, 50 sets of state laws, and many county and municipal laws and regulations, the author of the column strongly recommends that when specific legal questions arise, one should always consult an attorney, competent in the local law.*

► THIS ARTICLE CONCLUDES, FOR THE PRESENT, the references to generic names as appearing in recent resolutions of the policy making bodies of the American Medical Association and The American Pharmaceutical Association (see Law Column "Are Trade Names Necessary for Quality Drugs" August, 1960 issue of the AMERICAN JOURNAL OF HOSPITAL PHARMACY).

Nomenclature

House of Delegates—American Pharmaceutical Association, Cincinnati, Ohio, *August, 1959.*

"*Whereas,* research and rapid advancements in pharmaceutical chemistry have led to the development of complex organic compounds, and

Whereas, the pharmaceutical manufacturers have introduced into the drug trade hundreds of such new drug compounds during the past decade, and

Whereas, the nomenclature employed by the manufacturers in the information on these products provided to the retail pharmacist frequently requires clarification; therefore, be it

Resolved, the the American Pharmaceutical Association direct its Secretary to request the Pharmaceutical Manufacturers' Association to adopt a policy of having its members provide standard chemical names and structural formulas on all literature pertaining to new drug products; and be it further

Resolved, that the Pharmaceutical Manufacturers' Association be requested to adopt a policy of having its members feature on all products the *generic names* as well as brand names."

House of Delegates, American Pharmaceutical Association, Washington, D. C., *March, 1960.*

Whereas, pharmacy—the profession and industry—has been the target of attacks from many quarters as a result of derogatory misinformation arising from the Kefauver hearings, be it therefore

Resolved, that the American Pharmaceutical Association go on record as opposing any legislation or regulation which would

—Stifle the incentive to further progress in the discovery, development and distribution of drugs;

—Militate against the welfare of our profession and industry;

—*Restrict the free choice of drugs by prescribers;*

—Regiment against private practice by members of the health professions, and

—Undermine one of our nation's most precious assets—the highest health standards in the world today."

Note: The latter resolution was introduced as a result of one of the recommendations made by the Chairman of the House of Delegates in his House of Delegates address (March, 1960) which read:

> "In conclusion I would like to recommend that . . . In view of the fact that the whole of Pharmacy has been the target of attacks from many quarters as a result of derogatory misinformation arising from the Kefauver Hearings—this body go on record as opposing any outside regulations which would stifle the profession's and industry's incentive to further progress in research and development, militate against the welfare of our profession, restrict the free choice of drugs by physicians, regiment against good medical practice and undermine one of our Nation's most precious assets—the highest health standards in the world today."

This resolution is cited here, not because it indicates by indirection a departure from the stated policy of the American Pharmaceutical Association on generic or nonproprietary names, but to emphasize the fact that pharmacy respects the physician's choice of drugs prescribed by brand or generic names. It does not, of course, in any of the language surrounding the resolution, or in the resolution itself, place the Association in opposition to nonproprietary, U.S.P. and N. F. titles in prescribing.

CONTROL OF POISONINGS

edited by **ALBERT L. PICCHIONI,** *Director, Arizona Poisoning Control Program*

Intentional Inhalation of Vapors from Plastic Cement

► EIGHT INCIDENTS OF INTENTIONAL INHALATION of vapors from a commercial plastic cement involving teen-age boys in Phoenix, Arizona, have been made known to the Arizona Poisoning Control Information Center. The method of administration employed by the youths was to squeeze a portion of the contents of a tube of the cement in a handkerchief and then to inhale the vapors after placing the cloth over the face. One of the youths, who was encountered shortly after he inhaled the vapors, was found to be in a condition resembling inebriation. He was incoherent and staggered. The systemic effects of the vapors lasted for approximately one hour, after which time he had apparently recovered from all effects with the exception of a headache. A recent communication from the manufacturer producing the brand of plastic cement involved indicated that the active constituent of the product is toluene. This solvent is an aromatic hydrocarbon and produces basically the same toxic reactions as other solvents of this class, such as benzene and xylene. The toxic effects include local irritation, and central nervous excitation and depression. Exposure to toluene vapors is known to produce a transient euphoria, in addition to other effects such as giddiness, vertigo, headache, and ataxia. Although toluene does not produce the degree of bone marrow inhibition as does benzene, it may produce a mild macrocytic anemia.[1]

Management of Phenolphthalein Overdosage

The Phenolphthalein Research Institute has recently provided information concerning the treatment of phenolphthalein overdosage. It is the impression of this group that there is a tendency to employ excessive measures to counteract the supposed adverse effects of overdosage from this chemical agent. This practice is considered to be needless and is more likely to be fraught with harm than prove of benefit. The following suggestions for the management of phenolphthalein overdosage have been made:[2]

1. No gastric lavage is recommended. In the early stages it is unnecessary; later, it is useless. It may give rise to complications.
2. Vomiting should not be induced in children, as aspiration of particles vomited may cause complications.
3. Activated charcoal, U.S.P., in teaspoonful doses, suspended in milk, water or a carbonated beverage (but not in fruit juices) should be administered every 1 or 2 hours. If excessive laxation develops, administration of charcoal should be continued until the laxative action subsides.
4. If a very large quantity of phenolphthalein has been taken, it may be advisable to administer a therapeutic dose of castor oil. This will aid in eliminating the major portion of the phenolphthalein ingested. No saline cathartic, alkalies, glycerin, propylene glycol, alcohol, or other solvents of phenolphthalein should be given, as they may increase laxative action.
5. The person should remain quiet, but not confined to bed. The regular diet may be maintained with no restriction of fluids, except fruit juices.
6. Bismuth, kaolin or other bowel movement restraining drugs, except activated charcoal, are contraindicated. They prolong the action of the retained portion of the laxative by slowing up evacuation.

The above research group reports further, that the number of bowel movements following phenolphthalein overdosage seldom exceeds six in the first 24 hours, with two or three movements occurring after that time. The bowel action usually returns to normal not later than the third day. In the cases studied by this group, no instances of prostration, vertigo, dyspnea or any other systemic effects from phenolphthalein overdosage have been observed. Aside from laxation, the course is likely to be uneventful.

Phenolphthalein is a constituent of many proprietary cathartic preparations. Popular among these are Feen-A-Mint and Ex-Lax.

Acute Poisoning from Isopropyl Alcohol in Sponging

Isopropyl alcohol is sometimes used for tepid sponging of febrile children. A case report describing acute poisoning in a child following this procedure has recently appeared in the literature.[3] The case involved a

2½-year-old girl with a fever which accompanied an ear infection. In addition to drug therapy, alcohol sponging was prescribed. At midnight, the child was wrapped in a towel saturated with 12 ounces of 70 percent isopropyl alcohol. A second, dry towel was used to cover the first, and the patient was placed in bed with her aunt. A window in the bedroom was partly open. The following morning the child could not be aroused, and she was limp and totally unresponsive. Her pupils were small and did not respond to light; only corneal reflexes were observed. The patient became apneic for a short period and artificial respiration was required. Urinalysis revealed the presence of acetone in the urine, and the odor on the breath resembled acetone. The blood contained 130 mg. of isopropyl alcohol per 100 ml. The treatment was mainly supportive and included intravenous fluids, oxygen and antibiotics. An endotracheal tube was inserted because of the poor pulmonary ventilation. By the following morning the patient was fully conscious; however, she remained irritable and inactive for several more days. It was thought that the coma resulted from inhalation of isopropyl alcohol.

A similar case history reported[4] in 1953 involved a 22-month-old boy in whom acute poisoning also occurred as a result of inhalation of large quantities of isopropyl alcohol. In this case, bed linens drenched with 1¼ pints of isopropyl alcohol were used in the sponging procedure. Within five hours after the procedure, the child was in a comatose state such as that described for the above case. The blood of this child was found to contain 128 mg. of isopropyl alcohol per 100 ml.

In view of the potential hazards of employing alcohol in tepid sponging to reduce body temperature in fever, it would appear that water would be a more desirable liquid to use in the sponging procedure. The use of water should, indeed, be considered in preference to alcohol in febrile states in children resulting from acute poisoning from chemical agents.

When water is employed in sponging, water temperatures below 78°F. should probably not be used, not only because they are sometimes painful, but also because they generate reflex vasoconstriction which impairs their effectiveness. Ice packs and ice water baths are considered to be unnecessarily violent and dangerous.[5]

Esophageal Stricture from Accidental Ingestion of Clinitest Tablets

Ingestion of lye is a well-known cause of chemical burns and stricture of the esophagus. Approximately 50 percent of such burns and almost all strictures result from the ingestion of this agent.[6] One product which contains this caustic and is often found in homes is Clinitest, the tablets of which are frequently employed by diabetics in urine testing. Recently, two cases of accidental ingestion by children under 5 years of age of Clinitest tablets were reported.[6,7] In each case, a single tablet was ingested and esophageal stricture resulted. In one case, the stricture was complete and surgical intervention was required.

Clinitest tablets contain a combination of anhydrous sodium hydroxide, copper sulfate, citric acid, and sodium bicarbonate. If a tablet is ingested, the heat produced when the sodium hydroxide comes in contact with moisture and the caustic action of the lye can cause a thermal and chemical burn with resultant scarring and stricture of the esophagus. These effects are probably augmented somewhat by the astringent and irritant qualities of the copper sulfate in the tablet.

It is recommended that esophagrams be carried out to confirm the clinical impression of esophageal stenosis or stricture. If the patient has contact with a diabetic and no etiology is apparent, ingestion of Clinitest tablets should be considered.[6]

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Book Reviews

► **THE NATIONAL FORMULARY, ELEVENTH EDITION. Prepared by the Committee on National Formulary under the supervision of the Council, by authority of the American Pharmaceutical Association. Published by the American Pharmaceutical Association, Washington 7, D. C. 1960. Distributed by the J. B. Lippincott Company, Philadelphia, Pa. xxxii + 531 pp. 15 x 23 cm. Price $9.00.**

The new *National Formulary XI*, which becomes official October 1, 1960, represents the results of an ambitious revision program. Expansion of the scope of *N.F.* admissions to new drugs that have achieved wide use by the medical profession, but which were not admitted into the companion edition of the *U.S.P.*, reflects the advance in practical value of this official compendium. Among the 148 completely new items in *N.F.* XI are Acetaminophen (N-acetyl-*p*-aminophenol) (Category-Analgesic and antipyretic); Amisometradine (Category—Diuretic); Antazoline Phosphate (Category—Antihistaminic); Azacyclonol (Category—Psychotherapeutic agent); Benzestrol (Category—Estrogen); Benzpyrinium Bromide (Category — Parasympathomimetic); Benztropine Methanesulfonate (Category—Parasympatholytic); Dextromethorphan Hydrobromide (Category—Antitussive); Diphemanil Methylsulfate (Category—Anticholinergic); and Diphenadione (Category—Anticoagulant). These items, selected from those listed alphabetically under the letters A, B, C, and D, indicate the wide therapeutic spectrum that is covered. In reverse alphabetical order this interesting story reads the same. Zinc has finally yielded last place in the monograph section to Zoxazolamine (Category—Skeletal muscle relaxant; uricosuric). There is also Triacetyloleandomycin (Category—Antibiotic). It is clearly evident that *N.F. XI* reflects the accelerated turnover in the materia medica.

N.F. XI contains 815 mongraphs (*N.F. X* had 733); it has 285 new items (137 from *U.S.P. XV*). Its analytical procedures have been modernized and include column and paper chromatography, ultraviolet and infrared spectrophotometry, radioisotope tracer analysis, and countercurrent extraction. Its new two-column format makes reading easier; the page-top guide facilitates its use. The General Information section includes a really useful discussion of ophthalmic solutions with procedural guides for extemporaneous preparation. An important increase is noted in the 42 *N.F.* Reference Standards (*N.F. X* had 10). Most of the new reference standards are required in spectrophotometric analytical procedures. *N.F. XI* is smaller only in the number of pages. More material than ever has been included in 563 pages (*N.F. X* had 910 pages). This minor miracle was accomplished with the aid of experts at the Mack Printing Company. The two-column format, new type face, and style of arrangement is responsible for the elimination of much wasted space.

The value of the *N.F.* to pharmacists and others in the health professions is stepped up considerably in this latest edition. For example, hospital pharmacists will find a useful discussion of prescription balances on page 489, with a helpful chart which can be used to routinely check all departmental balances. Formulas for a number of clinical laboratory reagents and for staining solutions, together with information on sterilization, sterility tests and pyrogen tests make this edition of the *National Formulary* a useful and valuable compendium for the hospital pharmacist. Dr. Justin L. Powers, able Chairman of the National Formulary Committee, deserves high praise for a task well accomplished.

► **BRITISH PHARMACEUTICAL CODEX 1959. Published by Direction of the Council of the Pharmaceutical Society of Great Britain. Pp. XXIX + 1301. Price $14.00. The Pharmaceutical Press, 17 Bloomsbury Square, London W.C.I. Available in U.S. from The Rittenhouse Bookstore, 1706 Rittenhouse Square, Philadelphia, Pa.**

The seventh edition of the *British Pharmaceutical Codex* has been prepared by the Codex Revision Committee at the direction of the Council of the Pharmaceutical Society of Great Britain. Since publication of the first edition in 1907, the intent of the Codex Revision Committee has been to provide a reference book containing fundamentally information about drugs in common use throughout the British Commonwealth. Because of the rapid development of therapeutic agents and ancillary substances, the revision committee has found it necessary to exclude a number of monographs in order to maintain space requirements. The text, however, does include a large group of drugs which, while no longer accepted as being necessary by medical and pharmacological authorities, remain in considerable use. The problem of selection is therefore difficult and sometimes arbitrary. Monographs added to the seventh edition are in general for those agents whose value has been proven by pharmaceutical and clinical evidence. Older monographs retained are for those agents both of proven value and for those with little clinical evidence but which are prescribed frequently.

The functions of the *British Pharmaceutical Codex* are to not only provide information on drugs and pharmaceutical materials but to give specifications for those substances not included in the *British Pharmacopoeia*. The *Codex* differs from other texts of this type in that it presents information concerning the actions and uses of drugs based upon published evidence and the private experience of the various committees responsible. The monograph specifications provided are intended to characterize each drug, to limit significant impurities and to control the content of pure substances by an assay designed to give an accurate and reproducible result. Specifications are based upon pharmaceutical manufacturers' recommendations and upon the work of individual subcommittee members. All new and amended tests and assays have been tried out in the Society's laboratories.

In general, monographs contain an English main title with subsidiary title synonyms, translations of synonyms into Latin and English and abbreviations. Latin titles have not been created for new monographs. As in the sixth edition, monographs are arranged in alphabetical order of their English titles except where an inverted title would make location more feasible. For example, Dried Calcium Sulfate would be located between Calcium and Camphor; and Self-Emulsifying Monostearin would be found following Methylthiouracil and preceding Morphine Hydrochloride. When known and generally accepted, the chemical composition and structure is given at the head of the monograph. In addition solubility specifications and standards are provided.

The text is divided into six parts: General Monographs; Antisera, Vaccines and Related Products; Preparations of Human Blood; Surgical Ligatures and Sutures; and Formulary (dosage forms). The policy governing inclusion of monographs for the Formulary section has been unchanged; new formulae are only included if the substances named in them are freely available to pharmacists. Since most new drugs can be obtained only in the form of one or more

products of a single manufacturer, there is little reason for including such formulae. Of particular interest is the change in directions for preparing ophthalmic solutions. Previous procedures did not ensure against bacterial and mold growth in freshly prepared ophthalmic preparations. The *Codex* therefore specifies that the majority of solutions should be heated at 98° to 100° in the final container to destroy any pathogenic organisms present. Furthermore, the use of preservatives is also suggested provided the agent is compatible with the prescribed medicaments.

Of particular interest to practitioners are the appendices dealing with sterilization, isotonicity, milliequivalents and reagents. Quantitative tests for arsenic, lead, copper, alcohol, vitamins and nitrogen are also provided. Appendix XIV deals with the preparation of intravenous electrolyte solutions when prescribed in terms of milliequivalents.

The rapidly changing concepts in therapy have necessitated the addition of approximately 160 monographs of which approximately 70 are basic drugs. The formulary section has added more than 80 new formulae. In keeping with the rapid development and obsolescence of therapeutic agents, more than 280 monographs have been deleted from the previous edition. Many of the deletions are accounted for, however, by recent inclusion into the *British Pharmacopoeia*. Many others monographs, however, which represent oils, botanical remedies, plasters and draughts have been deleted because of disuse.

In an era which excludes the possibility of using only a limited number of texts as information sources for drug chemistry and pharmacology, the authors responsible for the seventh edition of the *British Pharmaceutical Codex* are to be commended for the prominent and superior role this edition assumes in supplanting the practitioner's ever changing and expanding reservoir of information. Its value is not limited to pharmacists in the British Commonwealth alone and should be a text available to students and practitioners everywhere.

HENRY J. DEREWICZ

▶ **PHYSICAL CHEMICAL PRINCIPLES IN PHARMACEUTICAL SCIENCE 1960. By Alfred N. Martin, Ph.D. 692 pages, 168 illustrations, 108 tables. Published by Lea & Febinger, Philadephia, Pa. Price $15.00.**

Although Physical Pharmacy has been an integral part of pharmaceutical curricula for several years, this book is the first adequate text designed for the course. Moreover, it a book which may be used as a source of information desired by the practicing pharmacist. For example, one chapter is devoted to Isotonic Buffered Solutions and includes both, the theoretical background and practical applications, along with worked examples. A review of this chapter should make it possible for a pharmacist to prepare adequate isotonic solutions when desired. The chapter on Rheology contains information useful in understanding and solving stability problems associated with disperse systems such as emulsions and suspensions. The section on Rate Processes contains a discussion of the kinetics of drug absorption and elimination which should be understandable to the person willing to put some effort into the study. This particular subject is currently being used in the design of such important dosage forms as "Spansules" and is therefore of great interest to the pharmacist.

The book is divided into twenty two chapters containing modern information on such subjects as: solubility, complexation, buffers, powder technology, colloids and interfacial phenomena. Although the reading is at times difficult the author has included background material such as a section on logarithms and graphical methods to aid the reader who is rusty in his mathematical techniques.

The book will probably be found most useful as a means of enriching one's background in order to understand the theoretical basis behind the great volume of empericism which we know as "practical" pharmacy.

JERE GOYAN

News

1961 Annual Meeting

Plans are being made for the 1961 Annual Meeting of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS which is scheduled to be held April 23 - 28 at the Hotel Sherman in Chicago, Illinois. The sessions will be held in conjunction with the Convention of the American Pharmaceutical Association.

Hospital Pharmacists who wish to contribute papers for presentation at the ASHP General Sessions are urged to communicate *immediately* with Mr. Paul F. Parker, Chairman of the SOCIETY's Committee on Program and Public Relations. Mr. Parker's address is: University of Kentucky Medical Center, Lexington, Kentucky. The deadline for receiving contributed papers for the 1961 Annual Meeting is January 1.

Geiger Promoted at Roche Laboratories

Promotion of Mr. Burns Geiger to the position of Director of the Hospital Department has been announced by V. D. Mattia, Jr., M. D., General Manager of Roche Laboratories, division of Hoffmann-La Roche Inc.

Mr. Geiger, who joined Roche Laboratories as an associate in education in the spring of 1960, is a graduate of George Washington University, Washington, D. C. He served in the U.S. Navy during World War II as a lieutenant communications officer.

After spending ten years in the practice of retail pharmacy, he joined the Veterans Administration and in 1948 became director of pharmacy service in the V.A.

For the past six years, Mr. Geiger was associated with Chas. Pfizer & Co., Inc. He began his career as a sales representative and, subsequently, became Director of Trade Relations, Director of Hospital Sales, Director of Promotions, and most recently, Customer Service Manager.

Mr. Geiger is a member of the ASHP.

Internship at University of Colorado

The School of Pharmacy of the University of Colorado, Boulder, has announced a Hospital Pharmacy Residency Program in cooperation with the Veterans Administration Hospital in Denver.

Candidates must be registered pharmacists and must be eligible for admission to the Graduate School. Requests for further information may be directed to Dean Curtis H. Waldon, School of Pharmacy, University of Colorado, Denver, Colorado.

Jefferson Medical College Hospital Pharmacy Alumni Meet

The Pharmacy Alumni of the Jefferson Medical College Hospital held a luncheon meeting at the Shoreham Hotel in Washington, D. C. during the Annual Meeting of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. Guests included individuals who have made special contributions to Jefferson's program in Hospital Pharmacy Administration. Among these were Dean Linwood Tice, Dr. Kenneth Avis and Mr. John Kramer of the Philadelphia College of Pharmacy and Science; Sister M. Gonzales of Mercy Hospital in Pittsburgh; Sister Mary John, Mercy Hospital, Toledo; ASHP President Clifton Latiolais and Mrs. Latiolais, Columbus, Ohio; ASHP Secretary Joseph Oddis, Washington, D. C.; Mr. Jack Heard, St. Francis Hospital, San Francisco; and Mrs. Evlyn Gray Scott, St. Luke's Hospital, Cleveland.

► DONALD R. CREAGAN has recently been appointed product sales manager in E. R. Squibb & Sons Sales Promotion Department. A native of Grand Rapids, Michigan, Creagan graduated from the University of Michigan with a B.S. degree and became a registered pharmacist in his home state. Before joining Squibb as a professional service representative in 1946, he had experience as a salesman and hospital pharmacist in addition to service in World War II as a chemical warfare officer. Mr. Creagan is affiliated with the ASHP.

► WILLIAM R. SHERIDAN has been appointed Promotion Manager for Ayerst Laboratories. He will be responsible for the planning and coordination of all promotional materials including pharmaceutical literature for Ayerst detailmen, special samples, displays, films and exhibits. He joined Ayerst as a salesman in 1946 in a territory with headquarters in Detroit, and was appointed Boston District Manager in 1952. In 1957 he left Boston to become General Sales Supervisor in the New York office.

Internship at University of California

The University of California (San Francisco) in cooperation with the University Hospital, the Veterans Administration Hospital, Oakland, and other participating hospitals in the Bay area has announced a two year (half-time) pharmacy internship which is available to students enrolling in the School of Pharmacy.

Pharmaceutical service for the Medical Center is provided by a staff of more than fifty, including eighteen pharmacists in the Hospital Pharmacy, the Manufacturing Laboratory, and the Parenteral Solution Laboratory. The training program for hospital phar-

Residents, interns and preceptors in hospital pharmacy training program at University of California. Shown left to right, front row: Donald C. Brodie, Ph.D., Professor of Pharmacy; Eric Owyang, Clinical Instructor; Walter Suda, Pharmacist, VA Hospital, Oakland; Stanley R. Marincik, Chief Pharmacist; and Charles E. Jackson, Clinical Instructor. Back row: Otmar Netzer and Kenneth Letcher, both Assistant Residents; Hubert Chan and Dwight Tousignaut, both interns; and Minoru Kashino, Assistant Resident

macists offers supervised experience in each of these areas, as well as in administration. A program is also provided for Residents and Assistant Residents in Hospital Pharmacy.

Applicants must be eligible for admission to the School of Pharmacy and hold a Bachelor of Science Degree or its equivalent from an accredited school or college of pharmacy. Further information may be obtained from Dr. Donald C. Brodie, University of California School of Pharmacy, San Francisco, California.

Cowles and Dilger Promoted at Parke-Davis

C. J. Cowles, a sales executive with Parke, Davis & Company, has been promoted to director of professional relations, according to Graydon L. Walker, vice president and director of U.S. sales and promotion for Parke-Davis. He succeeds John A. MacCartney, who has been named director of public relations for the world-wide pharmaceutical firm.

Mr. Cowles is a native of Watsonville, California and a graduate of Stanford University, where he studied pre-med and biological sciences. In 1951, he obtained an M.A. degree in business administration from Stanford and later that year joined Parke-Davis as a sales representative in the firm's San Francisco Branch.

In 1954, Cowles was transferred to Hawaii as a hospital service and sales representative, and later that same year was promoted to field manager for the San Francisco Branch, with headquarters in San Jose, Calif. He was transferred to Detroit in January, 1957, as assistant manager of the hospital and biological sales department. In 1958, Cowles was named manager of the department, holding that position until his present promotion.

Succeeding Mr. Cowles is Mr. J. C. Dilger who has been named manager of hospital and biological sales. Dilger, a native of Chicago and a graduate of Loyola University there, joined Parke-Davis in 1950 as a hospital service representative for the Chicago Branch. In 1954, he was named a Chicago branch field manager. Transferred to Detroit in 1955, Mr. Dilger was made assistant to the manager of market research in the sales division, and three years later was appointed assistant manager of hospital and biological sales, a post he held until his present promotion.

ACA Meetings for 1960

Henry H. Gregg, President of the American College of Apothecaries, recently announced the following meeting schedule for the College for the forthcoming year as voted upon by the A.C.A. Board of Directors.

The College will hold its Mid-Year Conference in conjunction with the American Pharmaceutical Association in Chicago in April, 1961.

As an innovation, a two day Eastern Regional Conference is being planned for Toronto, Canada on June 24 and 25, 1961 while the Annual Convention of the College will be held September 30, October 1 and 2, 1961, in San Francisco, California. It is the plan of the College to hold at least one Conference or Convention in each of the areas of the country each year.

Nominations Invited for 1960 Urdang Medal

Nominations for the next George Urdang Medal for distinguished historical writing will be accepted until 31 December 1960, according to the American Institute of the History of Pharmacy. Established by the Institute in 1952, on the occasion of the seventieth birthday of the noted historian of pharmacy and first Director of the Institute, George Urdang, the medal has been awarded six times since then.

The selection of an Urdang medalist is carried on through the world-wide organization of the International Academy for the History of Pharmacy, with its headquarters in Rotterdam, followed by ratification by the Committee on Awards of the Institute.

A postal card request addressed to the Institute office, 356 Chemistry Building, Madison 6, Wisconsin, will bring a nomination form that should be returned to Dr. P. H. Brans, Secretary-General, Académie Internationale d'Histoire de la Pharmacie, Niewe Binnenweg 420, Rotterdam-W. 2, The Netherlands.

as the Secretary sees it—

JOSEPH A. ODDIS, *American Society of Hospital Pharmacists, Washington, D. C.*

► PRESIDENT LATIOLAIS has kindly relinquished the president's page for this issue of the JOURNAL in order that I might personnally address you. I welcome this opportunity to greet you. I welcome this opportunity to express my gratitude on your vote of confidence in selecting me as your Executive Secretary and to assure you that I will endeavor to promote the objectives of the SOCIETY by implementing its programs to the best of my ability. Further, I welcome this opportunity to thank you for making it possible for me to serve hospital pharmacy specifically and pharmacy as a whole in this official capacity. Finally, I welcome this opportunity to extend an invitation to you to assist me in fulfilling the obligations and responsibilities associated with the office of the Executive Secretary.

Over the last several years, I have had the good fortune of meeting many of you at hospital pharmacy institutes, at state and national pharmacy and hospital association gatherings, and at the annual meeting of the SOCIETY. There are others whom I have met only through correspondence. Still, there are many of you whom I have not met and, in due course, hope to meet. Meanwhile, President Latiolais has generously afforded me the opportunity of officially greeting you in this column.

Recalling the mystery that surrounded each new professor who entered the classroom at the beginning of a school year, I am going to relate a little of my background, to describe for you the events leading to the action taken by the SOCIETY and the A.Ph.A. in creating the position which I now hold and to share with you some random thoughts regarding hospital pharmacy in general.

It was my privilege to attend the Duquesne University School of Pharmacy and my distinct honor to be a student of the late Dean Hugh C. Muldoon. I was attracted to hospital pharmacy almost immediately and received formal training under Sister M. Gonzales of Mercy Hospital, Pittsburgh, Pennsylvania. Following several positions with Sister, both as a member of her staff and as her assistant, I assumed the position of chief pharmacist at the Western Pennsylvania Hospital, also in Pittsburgh. In 1956, I was invited to join the staff of the American Hospital Association as a staff representative in pharmacy of the Council on Professional Practice.

The four years with the AHA provided a wonderful opportunity to meet with hospital administrators and state and metropolitan hospital association officials and to discuss with them the practice of pharmacy in hospitals. During these years, it was my good fortune to conduct the pharmacy institutes of the AHA held in cooperation with ASHP and A.Ph.A. It was also my good fortune to serve as Secretary of the Joint Committee of the AHA and ASHP. The Joint Committee serves as an excellent tool to achieve better understanding between hospital pharmacists and administrators. Some of the activities and worthwhile efforts of the committee were described by President Latiolais in this column several months ago.

It was at this time that the AHA inaugurated the Pharmacy Service Department which appears monthly in the first of the month issue of *Hospitals,* Journal of the American Hospital Association, and which I recommend to you.

In early 1960, I was invited to accept the position of Director, Division of Hospital Pharmacy of the American Pharmaceutical Association, following the resignation of Mr. Paul F. Parker, who served in this capacity since 1956 and with whom I had the pleasure of working rather closely during my time at the AHA. At the same time, I was named assistant secretary of the ASHP. In August of this year, Mrs. Gloria Francke officially announced her retirement after eleven years of devoted service to the SOCIETY and the profession, service given wholeheartedly and without recompense except for the joy and satisfaction that she derived from knowing that she was serving the profession. To fill the vacancy created by Mrs. Francke's retirement, the House of Delegates honored me by electing me to the position of Executive Secretary.

The series of events may be simply summarized by stating the end product—that a dual position has been created whereby a single person will serve as Executive Secretary of the ASHP and Director of the Division of Hospital Pharmacy of the A.Ph.A. I have been honored by being selected for this position. The official offices of the ASHP are located in the American Institute of Pharmacy, headquarters of the A.Ph.A., Washington, D. C.

Briefly, this gives you a bird's eye view of past activities and the events that transpired leading to the

agreement between the A.Ph.A. and ASHP to create a dual position, mutually beneficial to both organizations yet sustaining the autonomy and individuality of the respective positions.

Having taken this action, the SOCIETY has written another chapter of its exciting history. How successful will be this new venture is difficult to ascertain at this time. There is every reason to believe that the SOCIETY will be as successful in this program as it has been in such others as the *American Journal of Hospital Pharmacy,* the *American Hospital Formulary Service,* A.Ph.A. affiliation, the Audit of Pharmaceutical Services in Hospitals, joint and liaison committee activities, institutes and many others. The reasons for these past achievements are quite obvious. There exists within each member of the SOCIETY a compelling, enthusiastic spirit of cooperation and a self-sacrificing attitude that penetrates all obstacles or barriers to success. It was the knowledge that this philosophy prevailed that led me to accept the position offered. It was the knowledge that once the decision had been made to create the dual position, the entire SOCIETY would respond without hesitation to provide support, assistance and guidance as it has done so often in the past.

The SOCIETY has been unusually blessed over the years with competent and devoted leaders. Likewise, it has once again been blessed in having President Latiolais, Vice President Solyom and Treasurer Sister Berenice.

The majority of you have also demonstrated competence and devotion by accepting committee appointments which are always time consuming, exhausting and, in some instances, unrewarding. Some have not had the opportunity of serving the SOCIETY nationally but have, nevertheless, participated actively in one of the fifty-four affiliated chapters. It would be my hope that more and more of the members in time will have an opportunity to serve the SOCIETY at the national level.

In reviewing the questionnaire cards mailed to all members in July of this year in order to determine their interest in the work of the SOCIETY's committees, it was edifying to note that the immediate response to our request and the overwhelming return of the cards demonstrated without a doubt that the work that must be done will be done without complaint or hesitation.

I have already expressed my personal feelings regarding Mrs. Francke and Mr. Parker on other occasions. I again wish to praise them for their past achievements. In so doing, I wish to assure them and you that I will strive to carry out the duties of my office to the extent that the abilities with which I have been endowed will permit. At the same time, I feel reassured that each of you will continue to play your role, individually and collectively, and I warmly and sincerely extend to you an invitation to join me in writing still another chapter in the SOCIETY's history.

Joseph A. Oddis

Pharmacy Alumni of Jefferson Medical College Hospital met for a luncheon during the ASHP Annual Meeting in Washington. Guests included individuals who have made special contributions to Jefferson's program in Hospital Pharmacy Administration. Among these were Dean Linwood Tice, Dr. Kenneth Avis and Mr. John Kramer of the Philadelphia College of Pharmacy and Science; Sister M. Gonzales of Mercy Hospital in Pittsburgh; Sister Mary John, Mercy Hospital, Toledo, Ohio; ASHP President Clifton Latiolais and Mrs. Latiolais, Columbus, Ohio; ASHP Secretary Joseph Oddis, Washington, D. C.; Mr. Jack Heard, St. Francis Hospital, San Francisco; and Mrs. Evlyn Gray Scott, St. Luke's Hospital, Cleveland

SELECTED PHARMACEUTICAL ABSTRACTS

and summaries of other articles interesting to hospital pharmacists

edited by CLIFTON J. LATIOLAIS, HENRY J. DEREWICZ *and* LEO F. GODLEY

PARENTERAL SOLUTIONS, INSTRUCTION

Instruction in Parenterals in Pharmacy Schools, Bartilucci, A. J., Bull. Parenteral Drug Assoc. 13:3 (Sept.-Oct.) 1959 (College of Pharmacy, St. John's University, Jamaica, N. Y.).

The undergraduate professional curriculum provides the proper background and rudiments for further specialized training which is available in formalized undergraduate and graduate course(s) and in industry. The student is taught the pharmacology, chemical and physical properties, methods of sterilization and official types of parenteral containers. Advantage is taken of company-arranged tours to point out procedures of large scale production. Other important concepts taught are the importance of cleanliness, accuracy, labeling and the moral obligation to produce a product pharmaceutically elegant with stability, effectiveness, accuracy, etc. This material is normally covered by several courses rather than a specific parenteral course at the undergraduate level. Material related to parenterals is drawn together and amplified upon at the graduate level. Manufacturers of parenterals can and do contribute by excellent tours and equipment grants to institutions. Faculty members are made aware of the problems and needs in this area. People in industry can also help by assuming the responsibility of on-the-job training. In summary, pharmacy programs provide basic background and deficiencies in the qualifications of applicants can be lessened by the parenteral drug interests playing a larger part in the total pharmacy instructional program.

JAMES W. STOVER

PARENTERAL SOLUTIONS

Current Misconceptions in Parenteral Manufacturing, Avis, K. E., Bull. Parenteral Drug Assoc. 13:12 (Sept.-Oct.) 1959 (Philadelphia College of Pharmacy and Science, Philadelphia, Pa.).

The author has categorized certain selected misconceptions in parenteral manufacturing. The misconceptions regarding personnel are that any pharmacist should be able to make parenteral products without special training, and that hospital pharmacists cannot make high quality parenterals. The facts are that the pharmacist does require special training and the hospital pharmacist can make high quality parenterals. However, when economic reasons have priority over quality control, the result is almost certain to be inferior products. Fallacies relative to the working area and its control center around the rôle of face masks and ultraviolet lights. In the processes of preparation, misconceptions exist that a conductivity test measures organic contamination, that water containing the maximum total solids allowed by the USP can be successfully used in the formulation of all injections and that the type of filter used for a particular solution does not matter. Processes of preparing rubber closures may need re-evaluation in some cases. Another area of neglect is the adequate consideration of lag time in the heat sterilization process. Formulation misconceptions may be encountered where inadequate study is made of added substances with regard to their effectiveness for their intended use in a particular product. This is especially true of bacteriostatic agents which may be affected by pH, incompatibilities, sorption into the rubber closure, etc. Another misconception to which no one should fall prey is that he has attained a state of perfection for practical purposes and no longer must search for better methods and equipment.

JAMES W. STOVER

ULTRASONIC HYDROLYSIS

An Investigation of the Effect of Ultrasonic Waves on the Rates of Hydrolysis of Procaine and Butethamine Hydrochlorides, Fenn, G. D., and Belcastro, P. R., J. Am. Pharm. Assoc., Sci. Ed. 49:105 (Feb.) 1960. (School of Pharmacy, Purdue University, West Lafayette, Ind.).

A number of investigators have reported that ultrasonic vibrations initiate or accelerate chemical reactions. These effects, such as oxidation and depolymerization, have been attributed to the heating effect which may be as high as several hundred degrees. The possibility of using ultrasonic waves to accelerate certain chemical reactions applied to pharmaceuticals was investigated.

The effect of ultrasonic waves at a frequency of 400 K. C. per second on the rates of hydrolysis of procaine and butethamine hydrochlorides by comparison with noninsonated temperature accelerated hydrolysis was investigated. Ultrasonic oxidation of the compounds was prevented by the addition of an oxidant.

No significant differences were noted between the the rates of hydrolysis of insonated and noninsonated samples other than those attributable to slight increases in the overall temperatures of the insonated solutions.

Ultrasonic waves do not appear to have any significant influence on the rates of hydrolysis of procaine or butethamine under the experimental conditions employed in this investigation.

W. F. BERTZ

STERILIZING DISTILLED WATER BY UV LIGHT

Sterilization of Distilled Water by UV Light under Working Conditions of a Pharmacist, Lopatin, P. V., and Shimanko, A. I., Aptechnoe Delo (U.S.S.R.) 8, 6:48 (Nov.-Dec.) 1959 (Research Station of the Directory of Pharmacies, Moscow).

The authors suggest a simple apparatus for irradiation with ultraviolet rays which proved to be very suitable when sterilizing distilled water in working conditions of pharmacists' laboratory. The functioning of the apparatus obeys the following law:

$$F_\mu = \frac{Q.\&.K.\ \lg \frac{P}{P_o}}{1563{,}444\ \eta_\mu \eta_\rho}$$

The meaning of symbols is as follows:

F_μ=bactericidal performance of radiation generator (watts);

Q=quantity of distilled water to be sterilized (m^3/hour);

&=absorption coefficient of distilled water (cm^{-1});

K=resistance coefficient ($\frac{\mu W.sec}{cm^2}$);

P_o=quantity of bacteria in a unit volume of distilled water before sterilization;

P=quantity of bacteria in a unit volume of the same distilled water after sterilization;

η_μ=utilization coefficient of the bactericidal performance;

η_ρ=utilization coefficient of the intensity of bactericidal rays.

In the conditions of a pharmacy 0.04 $m.^3$ of distilled water was considered as a quantity to be used up in a day (200 liquid mixtures 200 ml. each). &=0.1 cm^{-1}, η_μ=0.9; and η_ρ=0.9.

It was found by bacteriological investigations that the quality of water sterilized by the above mentioned apparatus is very good.

HUBERT ŽÁČEK

PHARMACIST AS CONSULTANT

Pathology for the Pharmacist, (Part I), Huston, M. J., Pharm. J. (Canada) 92:14 (Nov.) 1959.

This paper is a discussion of some of the basic principles of pathology. Pathology may be defined as that branch of biological science which deals with the nature of disease, through the study of its causes, its process, and its effects, together with the associated alterations of the structure and function.

A pharmacist, to comprehend the methods and drugs used in treatment, must understand the nature of disease. Pharmaceutical curricula usually do not include courses in pathology *per se* and the pharmacist, as a result, is not as well versed in this subject as he should be. The pharmacy student does obtain some knowledge concerning disease incidental to the study of pharmacology and therapeutics. These two sciences would be more meaningful if complemented by a more thorough grasp of pathology. The pharmacist has the essential prerequisite of physiology. An understanding of the

normal (physiology) must come before the study of the abnormal (pathology). Medical courses in pathology usually put considerable emphasis on microscopy, requiring a background in histology and anatomy. However, training in pathology for the pharmacist would appear to be feasible without such detail.

It is anticipated that the future pharmacist will become more and more a consultant to the physician on drugs. Therefore, the pharmacist must be able to communicate with the doctor in his own language. Effective communication on the therapeutic use of drugs can occur only if the pharmacist understands the nature of the disease being treated.

Pathology for the pharmacist is outlined by the author in part one under the heading of predisposing factors in disease, immediate causes of disease, body defenses, and changes in disease.

W. F. BERTZ

DETERMINATION OF ALCOHOL IN TINCTURES

Determination of Strength of Alcohol in Tinctures, Bolotnikov, S. M., Shraiber, M. S., and Orlov, Yu. E., Aptechnoe Delo (U.S.S.R.) 9, 2:62 (March-Apr.) 1960 (Analytical Laboratory of the Chemical-Pharmaceutical Research Institute of Kharkov, U.S.S.R.).

The following method which is a modification of the method of Balovoine (Balovoine P., *Zeitschr. analyt. Chem. 89*, 230, 1932) is suggested for inclusion into the Ninth Edition of Soviet Pharmacopoeia:

First of all, the approximate concentration of alcohol in the tincture is determined by means of densimeter or pycnometer. Afterwards, the amount of extracted substances is found by evaporating the solvent from 10 ml. of the tincture and drying the residual until constant weight is attained; the result is related to 1 liter of tincture by computational procedures.

The strength of alcohol in the tincture is found according to the following relation:

$$X = A + \frac{10\ B}{A}$$

X=accurate concentration of alcohol in the tincture; A=approximate concentration of alcohol in the tincture; B=amount of extracted substances in 1 liter of the tincture.

As the determinations of density and amount of extracted substances are required usually *a priori* by pharmacopeias, the determination of the concentration of alcohol according to the described method involves mathematical operations only.

HUBERT ŽÁČEK

STEROID CHROMATOGRAPHY

16 Alpha-Hydroxy Steroids II. Partition Chromatography of Triamcinolone and Related Steroids, Smith, L., Foell, T. et al., J. Am. Pharm. Assoc., Sci. Ed. 48:529 (Sept.) 1959. (Chemical Process Improvement Department, Lederle Laboratories, American Cyanamid Co., Pearl River, N. Y.)

Paper chromatographic systems and column partition systems suitable for analyzing triamcinolone in pharmaceutical preparations and in extracts in biological samples are described. Comparative mobilities of related steroids are reported for various systems. Both qualitative and quantitative aspects of the chromatographic operations are described.

AUTHOR'S SUMMARY

IODINE DETERMINATION

The Polarographic Measurement of Iodine, Dandell, M. J., Edmondson, W. A., and Riedel, B. E., Pharm. J. (Canada) 92:48 (Nov.) 1959.

It has been reported that elemental halogens in acid media are reduced to the corresponding halide ions at a dropping mercury electrode of a polarograph. It was thought that a polarographic method for the determination of iodine in iodometric methods of analysis could be developed. It was anticipated that this method might be applicable to pharmaceuticals containing iodine in either large amounts or in trace amounts only. This paper describes the method and its application to weak solution of iodine B. P.

In the experimental procedures, polarograms were obtained with different concentrations of iodine. A regular diffusion was obtained with a well defined residual and limiting current. Measurements were made in concentrations from 1.269 mg. per liter to 126.9 mg. per liter. A series of determinations was then carried out on samples of weak solution of iodine B.P. A typical polarogram was obtained as anticipated. A qualitative determination on the trade preparation "BFI Powder" showed a typical polarogram for iodine, when a solution, prepared in mineral-free water, was treated in the same way as weak solution of iodine.

This method of iodometric analysis is advantageous as iodine may be detected polarographically in solutions containing other ions. It is possible to measure high concentrations of iodine by dilution, and it appears that the application of measurement to minute quantities is also possible. Only a small quantity of sample is required, analyses are easily and rapidly performed.

W. F. BERTZ

SOLUBILIZATION OF CAFFEINE, THEOPHYLLINE, AND THEOBROMINE

Effect of Inorganic Salts upon the Solubility of Caffeine, Theophylline, and Theobromine, Gusyakov, V. P., Aptechnoe Delo 8, 5:30 (Sept.-Oct.) 1959 (Dept. of Inorganic Chemistry, Medical Institute of Lvov, U.S.S.R.)

The solubilizing effect of various sodium and potassium salts upon caffeine, theophylline, and theobromine was studied. The former substances were utilized in concentrations up to 3 mols. The results indicate that rhodanide and iodide of both metals raise the solubility of the xanthine derivatives; chloride and sulphate show salting out effect whereas bromides are ineffective.

The following method for the characterization of the effect of solubilizing additive is suggested:

When the relation between solubility of the substance (S) and concentration of the added salt (C) is linear or nearly linear, it can duly be written as $S = S_o + KC$ (S_o means solubility in pure water). The slope of this linear equation $K = \frac{S - S_o}{K}$ indicates solubilizing power of the additive. If K is positive, then the additive increases the solubility of the studied substances; if K is negative then the salting out effect takes place; when no change in solubility is found then K is equal to zero.

HUBERT ŽÁČEK

BORIC ACID-SORBITOL COMPLEX

A Solubility Study of the Boric Acid-Glycerin Complex 1, Sciarra, J. J., and Elliot, D., J. Am. Pharm. Assoc., Sci. Ed. 49:115 (Feb.) 1960. (College of Pharmacy, St. John's University, Jamaica, N. Y.)

Glycerin has been used for many years as a solvent for boric acid. This solvent allows the use of approximately 20% of boric acid, whereas a saturated solution of boric acid in water contains approximately 5% of boric acid.

Sorbitol is also solvent for boric acid, forming a complex similar to that formed between glycerin and boric acid. The solubility of boric acid in sorbitol increased as the concentration of the sorbitol increased to a maximum solubility of about 19% of boric acid in 70% by weight of sorbitol solution at 25°.

The addition of water to a saturated solution of boric acid in glycerin will cause precipitation of boric acid, probably due to a change of solvent, resulting in a decrease in glycerin concentration. However, the addition of water to a saturated boric acid-sorbitol solution will not precipitate free boric acid. This indicates the increased stability of the boric acid-sorbitol complex as compared to the boric acid-glycerin complex.

The results of this investigation suggest the possible replacement of boroglycerin glycerite with a similar preparation utilizing sorbitol in place of glycerin, especially when a stock solution of boric acid is indicated. Bacteriological studies may indicate the possible use of this preparation for its antibacterial properties.

W. F. BERTZ

SUSTAINED RELEASE WITH RESINS

The Development of Liquid Antihistaminic Preparation with Sustained Release Properties, Smith, H. A., Evanson, R. V., and Sperandio, G. J., J. Am. Pharm. Assoc., Sci. Ed. 49:94 (Feb.) 1960. (School of Pharmacy, Purdue University, Lafayette, Ind.)

The use of ion exchange materials in medicine is as old as the medical profession itself. A good example is the use of kaolin and like substances as enteric adsor-

bents of toxins. In recent years, the use of synthetic ion exchange resins as medicinal agents has been investigated. The literature of this study indicates that the principle of sustained release of a drug from its resin-adsorbate might be applied to orally administered suspensions of the drug.

An antihistamine, methapyrilene, was chosen for this study of the feasibility of using cation exchange resins to obtain a controlled, sustained release of the drug. All of the resins were used in the acid form. It was found that sulfonic acid resins exhibited a greater relative capacity for adsorbing methapyrilene than the carboxylic acid resins, under the conditions of the experiment. However, all of the resins absorbed a sufficient quantity of methapyrilene per gram of dry resin to permit their use as medicinal carriers.

Results of experiments indicate that methapyrilene adsorbed on a sulfonic acid cation exchange resin possessed pharmacological activity at least equal, if not superior, to a solution of methapyrilene hydrochloride, as measured by the protection against histamine-induced asthma in the intact guinea pig.

W. F. BERTZ

ANTIHISTAMINICS IN BLOOD PRESERVATION

Use of Antihistaminics in Blood Preservation, Bican P., and Korychová E., Československá Farmacie (Czechoslovakia) 9, 4:186 1960 (Institute for Haematology and Blood Transfusion, Prague, Czechoslovakia).

In this work the expediency of the addition of antihistaminics to solutions used when conserving blood was studied. Antihistaminics produced by Czechoslovak pharmaceutical industry (Analergin-HCl i.e. (2-(N-phenyl-N-benzylamino)methylimidazoline-HCl) and Alfadryl-HCl (methyl-benzhydryl-β-dimethylaminoethylether-HCl) were considered. Their influence upon the conserved blood was judged by a part of the phosphorylation process in glycolizing human red blood cells by means of chromatography. It was found that the antihistaminics have no effect in blood conserving. For this reason, the authors of this paper do not agree with authors of other papers suggesting the addition of antihistaminics to solutions used when conserving blood.

HUBERT ŽÁČEK

FILTRATION OF INJECTABLE SOLUTIONS

Filtration of Injectable Solutions, Koniev, F. A., Aptechnoe Delo 8, 5:64 (Sept.-Oct.) 1959 (Chimicopharmaceutical Research Institute, Kharkov, U.S.S.R.).

Fundamentals of the filtration process of injectable solutions were studied by means of a filter of a special construction. It was found that this filtration is one of the so called "closed" type, i.e. sediment is formed on the external filtering surface. The following equation characterizes this type of filtration:

$$Kt = \frac{t}{V} - \frac{1}{S_o}$$

V=volume of the liquid passing through the filter - ml./cm²;
t=duration of filtering process/min.;
S=filtration velocity at time t - cm./min.;
K and $\frac{1}{S_o}$ = constants.

The values of the constants with respect to the most common injectable solutions were determined. K and S_o vary between 2.07 and 10.03, and between 10^{-8} and 10^{-5} respectively. Based on his results, the author suggests a new type of filter of high efficiency which has many advantages over the usual vacuum and pressure filters.

HUBERT ŽÁČEK

RELEASE OF SOLUBLE MEDICAMENTS

The Influence of Some Suspending Agents on the Release of a Soluble Medicament from Solution, Redman, G. D., Christian, J. E., and Sperandio, G. J., J. Am. Pharm. Assoc., Sci. Ed. 49:98 (Feb.) 1960. (Purdue University, School of Pharmacy, Lafayette, Ind.)

A number of new approaches to the preparation of dosage forms for oral administration have been made which are intended to produce a sustained level of drug action. Most of these dosage forms were encapsulated or tableted medicinal substances. Therefore, this project was initiated in an attempt to find a way to prepare liquid medications with sustained release properties.

The investigation utilized iodine^{131}-labeled iodine ion to study the effect of 10 different suspending agents on the dialysis of the iodide ion through a semipermeable membrane. This procedure was proved by this investigation to be a satisfactory method for comparing the influence of suspending media on the dialysis of a soluble compound.

Different suspending agents were shown to affect the rate at which the iodide ion dialyzes from the solution. Varying the concentration of the suspending agent has a non-linear effect on the release of the iodide ion. Release rates indicate that the nature of the suspending agent is a variable in affecting the release of the compound.

This work indicates that the use of selected suspending agents modifies the release rates of certain soluble drugs from a solution.

W. F. BERTZ

CURRENT LITERATURE

. . . also calling your attention to the following articles appearing in recent hospital and pharmaceutical journals

. . . . . .

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—Dispensing

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Narinian, George: Drug Survey Points Up Need For Price, Markup Uniformity, *Hosp. Topics* 38:57 (Aug.) 1960.

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Heller, William M.: Half of Your Students Will be Hospital Pharmacists, *Am. J. Pharm. Ed.* 24:309 (Summer) 1960.

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Sister Joseph Ignatia: Setting up a Hospital Pharmacy—Location and Layout, *Hosp. Pharm.* (Canada) 13:157 (July-Aug.) 1960.

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Jeffrey, Louis P.: The Pharmacy Newsletter—Voice of the Department, *Hospitals* 34:57 (Sept. 1) 1960.

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DRUG EVALUATIONS

by the Council on Drugs of the American Medical Association

► THE FOLLOWING MONOGRAPHS and supplemental statements on drugs have been authorized by the Council on Drugs of the American Medical Association for publication and inclusion in *New and Nonofficial Drugs*. They are based upon the evaluation of available scientific data and reports of investigations.

The issue of the *Journal of the American Medical Association* from which each monograph has been taken is noted under each monograph. Monographs in this issue of the JOURNAL include those published in the *A.M.A. Journal* for June 4* and June 11.

Notice

New and Nonofficial Drugs 1960 is now available from your local bookstore and from the publishers, J. B. Lippincott Company, Philadelphia, Pa. This 1960 edition contains monographs of drugs evaluated by the Council on Drugs of the American Medical Association and published in the Journal of the A.M.A. to October 17, 1959. The indexes listed below contain those drugs evaluated and published between October 24, 1959 and June 11*, 1960.

Index

TO DRUGS EVALUATED IN THIS ISSUE

Index

TO EVALUATED DRUGS AND ARTICLES IN THE FEBRUARY, MARCH, APRIL, MAY, JUNE, JULY, AUGUST AND SEPTEMBER ISSUES OF THE AMERICAN JOURNAL OF HOSPITAL PHARMACY.

*Part of the material from this series which was included in the June 4 issue of the *J.A.M.A.* appeared in the September issue of THIS JOURNAL.

NEW AND NONOFFICIAL DRUGS

The following descriptions of drugs are based on available evidence and do not in any case imply endorsement by the Council.

H. D. KAUTZ, M.D., *Secretary.*

Tetrahydrozoline Hydrochloride — Visine® Ophthalmic Use of

►TETRAHYDROZOLINE HYDROCHLORIDE is a potent sympathomimetic agent which was described previously for intranasal instillation in the symptomatic treatment of inflammatory hyperemia and edema of the nasal mucosa; for this purpose, it is marketed under the trade name Tyzine Hydrochloride. (See the monograph on tetrahydrozoline hydrochloride in New and Nonofficial Drugs.) The Council subsequently has evaluated the usefulness and safety of the drug for use as an ophthalmic decongestant. Preparations intended for use in the eye are marketed on an over-the-counter basis under the trade name Visine.

When instilled into the conjunctival sac, solutions of tetrahydrozoline cause vasoconstriction of peripheral vessels. As measured by blanching of hyperemic conjunctiva, the onset of vasoconstriction is apparent within several minutes and persists for about four hours. Clinical reports indicate that the drug is useful as an ophthalmic decongestant for the symptomatic relief of conjunctival edema and hyperemia secondary to ocular allergies, minor irritations, and so-called nonspecific or catarrhal conjunctivitis. Beneficial effects include amelioration of burning, irritation, pruritus, soreness, and excessive lacrimation. Rebound vasodilation and congestion have not been reported. In approximately 2% of patients, a transient burning or stinging sensation is experienced when the drug is instilled into the eye; there is no evidence that it induces sensitization.

Ophthalmic solutions of tetrahydrozoline hydrochloride do not affect reaction to light or accommodation. On the basis of its other sympathomimetic properties, however, some degree of mydriasis is to be expected. Thus, in experimental animals, it is possible to produce a slight pupillary dilation. One clinical investigator also reported instances of a dilation of 0.5 mm. in the pupils of three of eight patients studied. However, the majority of clinical observers, using the drug in a large number of patients with and without glaucoma, have been unable to detect any significant increases in pupillary size or intraocular pressure. Hence, the likelihood of inducing acute glaucoma in patients in whom the iridocorneal angle is narrow seems quite remote. Pending conclusive confirmation of this fact, however, caution is enjoined against use of tetrahydrozoline in any person with serious eye diseases such as glaucoma. This warning, carried on the label of ophthalmic solutions, is particularly appropriate since the drug can be obtained without a physician's prescription.

For ophthalmic use, two or three drops of a 0.05% solution of tetrahydrozoline hydrochloride is placed in each eye two or three times daily.

The Council voted to expand the monograph on tetrahydrozoline hydrochloride in New and Nonofficial Drugs to include the foregoing comments concerning its proposed use as an ophthalmic decongestant.

Pfizer Laboratories, Division of Chas. Pfizer & Co., Inc., cooperated by furnishing scientific data to aid in the evaluation of the ophthalmic use of tetrahydrozoline hydrochloride.

***J. Am. Med. Assoc.* 173:677 (June 11) 1960.**

COUNCIL ON DRUGS

Antimicrobial Therapy In Injured Patients

WILLIAM A. ALTEMEIER, M.D.

and

JOHN H. WULSIN, M.D., *Cincinnati*

► IT IS A WELL-ESTABLISHED fact that hemorrhage, shock, impairment of respiration, and infection are the complications most dreaded in injured patients.[1] Wounds of violence are particularly prone to develop infection because of their gross contamination, the presence of large areas of devitalized tissue and retained foreign bodies (fig. 1), the involvement of regions particularly susceptible to infection, the frequent association of vascular injuries, and delayed or faulty surgical therapy.[2] The development of infection in wounds increases the period of morbidity, produces further destruction of tissue, suppresses the process of healing, and may have a significant effect on mortality.[3] Tissues destroyed by bacterial invasion are usually replaced by scar tissue which may affect function as well as cosmetic appearance.

Fig. 1.—Crushing injury resulting from train accident. Note traumatic disarticulation of head of femur, extensive damage of soft tissues, laceration of femoral arteries, and gross contamination, conditions which predispose to development of severe wound infection.

General Considerations

Unfortunately, infection, the greatest enemy of wound healing, continues to be a serious problem, aseptic technique and antibiotic therapy notwithstanding. The primary basis of this form of infection is the successful growth of micro-organisms within the wound itself and their invasion of the physiological interior of the body. Experience has shown that bacteria may be present in a wound without producing clinical evidence of infection and that certain factors influence their growth and invasion. Normal tissues have a remarkable resistance to micro-organisms and their effects, whereas irritated or devitalized tissues have limited or little capacity of resistance.[4] Dead tissue remaining in a wound invites and supports the growth of virulent as well as relatively nonvirulent or saprophytic organisms.

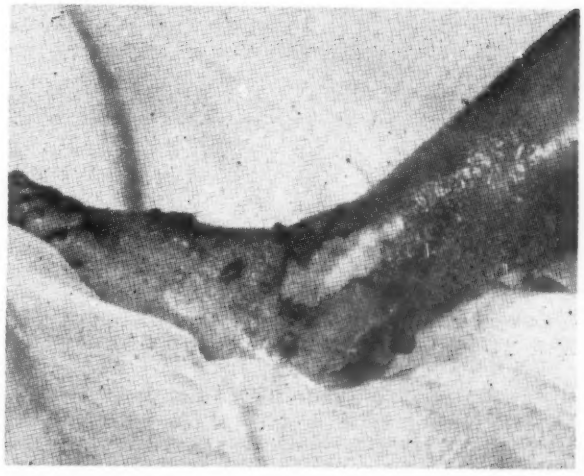

Fig. 2.—Necrosis of tissue produced by severe infection developing in small wound of the leg.

The physical condition of the injured patient may also be an important predisposing factor to infection. General debility, severe dehydration, prolonged shock, malnutrition, exhaustion, metabolic disorders such as uncontrolled diabetes or cirrhosis, marked anemia, steroid therapy, leukemia, or recent and extensive x-ray irradiation may lower his general or local resistance sufficiently to permit bacterial invasion.[5]

Thoughtful consideration of the foregoing facts leads to certain general conclusions. The development of local wound infection depends primarily on the altered physiological state of the wound. If devitalized tissue is permitted to remain or develop in the wound, bacterial growth and infection are probable, in the face of the concomitant contamination (fig. 2). It may be assumed that antibacterial therapy is necessarily adjunctive treatment and of secondary importance to early and adequate operation.[6]

The chief benefit of antimicrobial therapy lies in the attenuation, limitation, or control of infection by residual micro-organisms in the wounds after débridement and operative repair, or in the localization of infection developing within wounds in which surgical treatment is necessarily inadequate, delayed, or impossible. Clinical experience has repeatedly shown that all of the various antibacterial agents must be used intelligently to obtain their full effects. Failure to observe certain established principles in the management of injured patients with antimicrobial agents may result in incomplete or limited effects or even failure. The purpose of this dis-

From the Department of Surgery, University of Cincinnati College of Medicine and the Cincinnati General Hospital.

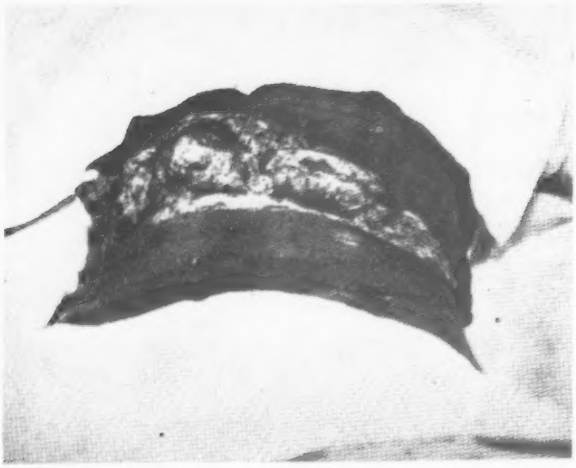

Fig. 3.—Fulminating anaerobic cellulitis of abnormal wall originating from left inguinal wound. Radical incision and drainage were mandatory to arrest rapid spread of infection.

cussion is to review these factors as well as the indications, methods, value, and limitations of practical antibacterial therapy in wounded patients for the prevention or treatment of various infections which may complicate trauma.

Special Considerations

Accurate and Complete Diagnosis.—The importance of a correct clinical diagnosis and evaluation of the injured patient's condition is fundamental. Careful examination should be done to determine the cause, location, nature, extent, and duration of the injuries. The existence of shock and the presence of special wounds such as crushing injuries, or penetrating wounds of the abdomen, chest, or central nervous system should be noted. General factors which might contribute to bacterial invasion such as diabetes mellitus or concomitant steroid therapy should be detected, if present. Additional valuable information can be gained as to the probable types of contaminating or infecting bacteria. Observation may suggest the kind of infection and whether it is localized or invasive, mild, serious, or fulminating. Immediate examination by smear and culture of exudates obtained from infected areas are also recommended for additional diagnostic information.

Proper Timing of Operative Treatment.—If only bacterial contamination exists in wounds, prompt surgical excision and removal of all the devitalized tissue, clotted blood, and foreign bodies within six to eight hours after injury are most important. Antimicrobial therapy should be started before operation, however, and continued postoperatively. If bacterial infection has been established, surgical excision of the infection is generally impossible. Other necessary operative procedures may be delayed to advantage until the invasive qualities of the infection have been overcome by antimicrobial therapy or have been limited by less extensive procedures, such as incision and drainage of abscesses or areas of necrotizing cellulitis, or the removal of sloughing tissue, sequestra, or foreign bodies. In certain infections, such as gas gangrene, anaerobic cellulitis, and acute hemolytic streptococcic gangrene, emergency surgical decompression by radical incision and drainage may be necessary (fig. 3).

Selection of Effective Antibacterial Agents.—The selection of the antibiotic agent should be made on the basis of its effect on the contaminating or infecting bacteria presumed or known to be present. When possible, one or two effective agents should be used instead of a "shotgun" mixture of three or more agents. Evidence indicates that the use of multiple agents will not prevent the development of infection by organisms such as the hemolytic Staphylococcus pyogenes var. aureus and the various gram-negative bacilli if the local conditions are favorable. Of more importance is the fact that infection emerging under the screen of multiple antibiotic therapy will be caused by bacteria resistant to the antibiotics used as well as to other related antibiotic agents. Antibiotic sensitivity tests are recommended in the selection of antibiotic agents for the treatment of serious or prolonged infections whenever possible. It is important, however, to keep in mind the possibility of error in results of sensitivity tests done by the commercial disk method (fig. 4).[7]

Adequate Dosage.—The dose of the antibiotic agent chosen should be sufficiently large to produce antibacterial concentrations in the blood, tissues, and exudates at the sites of injury or infection. In addition, the duration of therapy should be sufficiently long to permit the natural defense mechanisms of the body to dispose of the inhibited, but often still virulent, bacteria. Since most agents exert only a bacteriostatic effect, failure to continue treatment long enough may result in the delayed appearance or exacerbation of an infection. Experimental and clinical data also suggest that progressively larger doses of some of the antibiotics, notably penicillin, have an increasingly greater antimicrobial effect (fig. 5).[8]

Method of Administration.—Wounds of violence are frequently associated with shock produced by one or more causes. This complication may affect the method chosen for the administration of antibacterial agents. If shock is present, absorption of antibiotic agents given by intramuscular or oral routes may be retarded, inadequate, or capricious.[9] For this reason the intravenous route is recommended until the shock has been adequately treated and controlled. The local application of chemotherapeutic agents to wounds is seldom indicated in the management of patients with acute injuries and is not recommended.

Early Treatment.—The earlier that antibiotic therapy is started after injury the better its effects. Generally speaking, the antimicrobial agent selected should be administered intravenously promptly after the seriously injured patient is admitted to the hospital and before he is taken to the operating room. If infection has already developed, early therapy gives the best chance of obtaining rapid and prompt control of the invasiveness of the process, with either spontaneous resolution of the lesion or limitation of the bacterial slough to

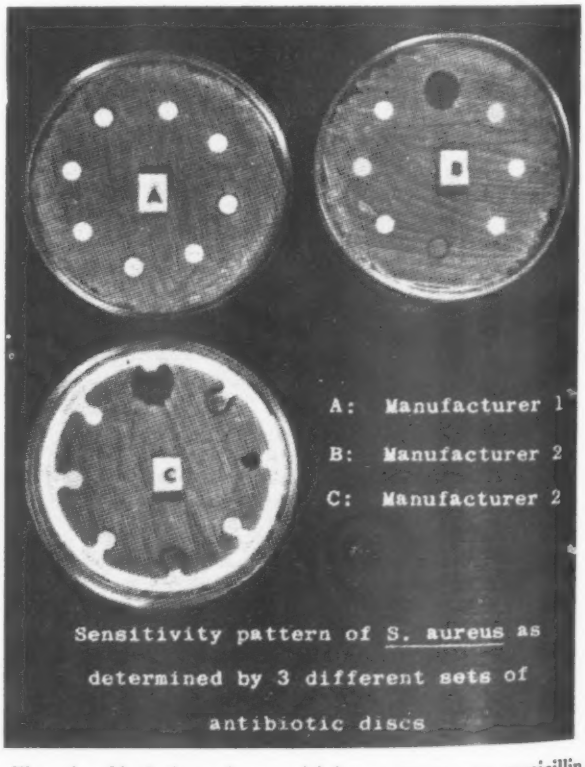

Fig. 4.—Variations in sensitivity patterns to penicillin, chloramphenicol, oxytetracycline, and tetracycline for hemolytic Staphylococcus pyogenes var. aureus as determined by commerical disk method.

a minimum.[10] Delayed or late treatment usually is less effective, but it often permits localization of the process and indicated surgical procedures when the patient's general condition has been restored to a normal or a near-normal state.

Complications.—A variety of complications or untoward reactions may develop in patients undergoing antibiotic therapy with any of the agents.[11] It is important for the clinician to be informed as to their nature and to be alert for their occurrence. Those complications caused directly by the antimicrobial agents include (1) toxic reactions related to the type and amount of drug given, (2) hypersensitivity reactions, and (3) idiosyncrasies.[12] Although toxicity of the various agents differs considerably, each of the drugs has been shown to be capable of producing one or more types of reaction. Those produced by overdosage can be readily prevented or controlled, but the accumulation of high serum concentrations in aged or debilitated patients can be overlooked easily. Those secondary to hypersensitization of the patient are becoming of increasing importance, particularly in the instance of penicillin. Fortunately, idiosyncrasies to these agents including chloramphenicol (Chloromycetin) are exceedingly rare.

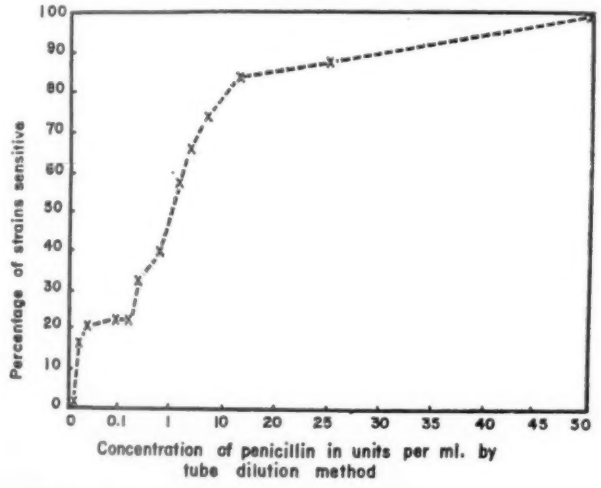

Fig. 5.—Curve indicating increasing percentage of susceptibility of 48 strains of hemolytic Staphylococcus pyogenes var. aureus to progressive concentrations of penicillin, with 85% being sensitive to 12.5 units of penicillin per cubic centimeter (ml.).

Another complication of increasing importance is the secondary or superinfection caused by antibiotic-resistant bacteria. The suppression of sensitive bacteria in mixed infections by antibiotics may be followed by a marked change of the bacterial flora in the wound or in the systemic tracts. Under these circumstances bacteria which are normally of lesser virulence may become invasive and may even invade the blood stream. Such infections have generally been produced by the hemolytic Staph. pyogenes var. aureus and gram-negative bacilli such as Proteus vulgaris, Pseudomonas aeruginosa, Escherichia coli, and Aerobacter aerogenes.

Another complication which may occur in the seriously injured patient is the masking of infection which develops in the vicinity of the wound or elsewhere in the body. This masking makes the recognition and localization of the infection difficult.

Supportive Therapy.—In recent years the importance of adequate supportive treatment in injured patients undergoing antibiotic therapy has been emphasized. The full therapeutic effect of the antibacterial agent will not be obtained if serious derangements in local and general physiology are overlooked or uncorrected. More recent evidence indicates that the effectiveness of certain antimicrobial drugs, particularly chloramphenicol, can be significantly enhanced by the concomitant use of pooled immune serum globulin in case of overwhelming or serious long-standing infections.

Prophylaxis in Acute Trauma

Prophylactic antibacterial therapy is recommended promptly for all patients with serious wounds of violence such as major open soft tissue wounds, compound fractures, penetrating wounds of the abdomen, the chest, or both, penetrating wounds of the central nervous system, injuries involving the oral or pharyngeal cavities, and injuries of the perineum. The antimicrobial therapy should be given systemically as soon after injury as possible and continued postoperatively. If the patient is in shock, the chemotherapeutic agent should be administered intravenously for reasons described previously.

Soft Tissue Wounds and Burns.—No antibiotic therapy is recommended for trivial or minor injuries. The following agents are recommended for initial prophylaxis in serious or severe injuries: 1. Aqueous sodium penicillin G or potassium penicillin G (Dramcillin, Dropcillin, Penalev, Pentids, Potassium Penicillin G), 250,000 to 500,000 units may be given intramuscularly or intravenously every six to eight hours for five days in patients who are not sensitive. Erythromycin (Ilotycin) ethyl carbonate or erythromycin (Erythrocin) lactobionate may be used as an alternate. It is questionable whether any significant additional protection can be obtained from the combined use of penicillin with a broad-spectrum antibiotic. Accumulative data indicate that invasive infections by beta-hemolytic streptococcus and pneumococcus can be successfully prevented by antibiotic prophylaxis, but there is little or no similar evidence of successful prevention of infections by the hemolytic Staph. pyogenes var. aureus, Ps. aeruginosa, P. vulgaris, Esch. coli, and other gram-negative bacilli. 2. If desired, one of the broad-spectrum antibiotics such as chloramphenicol, demethylchlortetracycline (Declomycin), tetracycline (Achromycin, Panmycin, Polycycline, Steclin, Tetracyn) hydrochloride, chlortetracycline (Aureomycin) hydrochloride or oxytetracycline (Terramycin) hydrochloride may be given systemically in doses of 500 mg. every eight hours, or 250 mg. every four hours, and continued for three or four days. The need for such therapy is then reconsidered and continued, discontinued, or modified as indicated by the presence or absence of infection. 3. For patients with less severe wounds, the oral route may be used to advantage for the administration of either penicillin or the broad-spectrum agents.

Compound Fractures.—The same general plan of prophylaxis as outlined in the preceding paragraph is generally useful. In patients with wounds exhibiting extensive tissue necrosis along with compound fractures, larger doses of penicillin, up to 1,000,000 units of an aqueous soluble salt of penicillin G every three hours, may be indicated.

Penetrating Wounds of Abdomen.—There is considerable evidence that antimicrobial therapy is of great prophylactic value in preventing death from peritonitis and sepsis in patients with penetrating wounds of the abdomen. Adequate systemic antimicrobial therapy used in conjunction with early surgery has reduced the mortality in such patients from 40 to 60% to 9 to 11% and has minimized peritonitis as a cause of death. It is recommended that the antimicrobial therapy be given preoperatively, intravenously, and as soon after the patient's admission to the hospital as possible in an effort to inhibit bacterial growth intraperitoneally and to provide an antibacterial concentration in the peritoneal fluid at the time of operation.[13]

The following plan has been used at the Cincinnati General Hospital during the past 10 years: 1. One million units of an aqueous soluble salt of penicillin G in sodium chloride injection or 5% dextrose in water for injection is administered intravenously as soon after the patient's admission to the receiving ward as possible and as part of his preoperative resuscitation therapy. 2. At operation, no antimicrobial agents are instilled into the peritoneal cavity. 3. Postoperatively, 500 mg. of one of the tetracyclines or chloramphenicol is administered intravenously along with penicillin. 4. An aqueous soluble salt of penicillin G in doses of 250,000 to 500,000 units is recommended every six hours intramuscularly for five days.

One of the tetracyclines or chloramphenicol in doses of 500 mg. is given intravenously every 12 hours for four to six days. At the end of this period, antibiotic therapy is discontinued if there is no obvious infection, continued until the infection has been controlled, or modified as indicated by the emergent antibiotic-resistant infection.

Penetrating Wounds of Chest.—A plan of antibacterial prophylaxis similar to that described in the section on penetrating wounds of the abdomen may be used.

Therapy of Established Infections in Acute Trauma

Therapeutic antimicrobial therapy is of considerable value in the control of established infections developing in the injured patient when started early and based on the various factors or principles discussed previously under special considerations.

Local Infection.—For patients with slight or moderate local infection in whom no serious infection is anticipated, the same antimicrobial dosage schedule is recommended as that described for prophylactic use in soft tissue wounds. This plan should be modified on the basis of any demonstrated antibiotic resistance of the bacterial infections which emerge under the prophylactic antimicrobial treatment.

Invasive Staphylococcic and Streptococcic Infections.—In injuries with established invasive infections localized to the tissue surrounding the wound, or the regional lymphatics and lymph nodes, antibiotic therapy should depend on the infecting bacteria. In hemolytic streptococcic or staphylococcic infections of moderate severity or regional invasiveness, the choice of the antibiotic treatment may be made from the following agents: (1) an aqueous soluble salt of penicillin G, 100,000 to 500,000 units every four to six hours intramuscularly in the absence of patient sensitivity to penicillin; (2) for penicillin-resistant staphylococcic infections, chloramphenicol, demethylchlortetracycline, tetracycline, oxytetracycline, chlortetracycline, or erythromycin in doses of 250 mg. orally every four hours, depending on the demonstrated sensitivity results; (3) an aqueous soluble salt of penicillin G in large doses of 1,000,000 units every three or four hours (fig. 5); (4) vancomycin (Vancocin) hydrochloride administered parenterally in doses of 250 mg. every six hours; this agent is still in short supply and relatively expensive, however; and (5) continuation of adopted therapy until infection is under control and fever and white blood cell counts are normal for five to seven or more days.

In systemically invasive or fulminating streptococcic and staphylococcic infections, the same plan may be adopted, with consideration of increasing the dosage, shortening the interval between doses, and administering by the preferential intravenous route.

Mixed Bacterial Infections.—In severe infections caused by fecal bacteria, such as peritonitis, retroperitoneal cellulitis, crepitant cellulitis, putrid empyema, and mixed infections of the buttocks, thigh, or perineum, essentially the same antimicrobial agents may be used as in prophylaxis of penetrating wounds of the abdomen, plans 1, 2, and 3. The broad-spectrum antibiotic should be selected on the basis of demonstrated sensitivity of the infecting bacteria and should be given in larger doses of 500 mg. every four to six hours. Chloramphenicol has been particularly effective in our experience when used with penicillin and immune serum globulin given intramuscularly. The importance of recognizing and draining intraperitoneal or retroperitoneal abscesses masked by antibiotic therapy cannot be overemphasized.

Clostridial Infections.—In established clostridial myositis or true gas gangrene, the choice of effective antibiotic therapy may be made from the following regimens: 1. Chlortetracycline, oxytetracycline, tetracycline, or chloramphenicol may be given intravenously in doses of 500 mg. every six to eight hours. Both experimentally and clinically, however, the tetracyclines have been the drugs of choice in this serious infection.[14] 2. An aqueous soluble salt of penicillin G in doses of 1,000,000 units given intramuscularly every three hours may also be effective. As seen in figure 6, it has been shown experimentally that increasingly large doses of penicillin G have

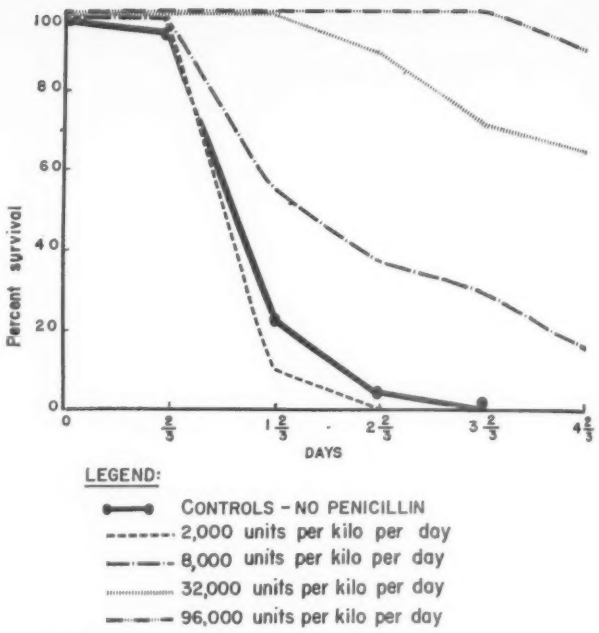

Fig. 6.—Effect of immediate penicillin therapy on experimental gas gangrene.

a progressive effect in controlling experimental clostridial infections and in decreasing the incidence of death.

For patients with clostridial cellulitis, the same two plans of antimicrobial treatment are used at the Cincinnati General Hospital.

Tetanus.—There is no scientific evidence to indicate that antibiotics have any effect on circulating tetanus toxin or toxin fixed in the central nervous system. There is also lack of evidence to indicate that antibiotic therapy can affect mortality except through the control of secondary infection, such as pneumonitis or associated bacterial infections of the wound. It is usually agreed that patients with tetanus should be given antibiotic therapy in an effort to prevent or control the pneumonitis which frequently occurs as a result of the prolonged sedation, aspiration of the increased volume of secretions during convulsions, or impairment of respiration.

Serious Pseudomonas (Pseudomonas aeruginosa) Infections.—These infections may be treated with the following antibiotics: 1. Polymyxin B (Aerosporin) sulfate, 2.5 mg. per kilogram of body weight, may be given in 24 hours, the amount being divided into three or four doses which are administered under close observation every six or eight hours for a period of five to seven days. Pain at the site of intramuscular injection may be appreciable, but it can be reduced by the addition of a 1% procaine solution as a diluent. Because of the toxicity of polymyxin B sulfate, a daily dose of 200 mg. should not be exceeded, and patients undergoing therapy should be observed closely for signs of renal or neurological toxicity. Few, if any, strains of Pseudomonas are resistant to polymyxin B sulfate in concentrations of 12.5 mcg. per cubic centimeter. 2. Chloramphenicol, tetracycline, oxytetracycline, chlortetracycline, or demethylchlortetracycline may be used, but they are generally less effective.

Septic Shock.—Occasionally, patients with injuries will develop a state of clinical shock not attributable to the usual causes, such as hemorrhage or trauma. This condition, when associated with proved serious infection, may be septic shock which characteristically occurs two to five days after injury. In studies at the Cincinnati General Hospital,[15] it is interesting to note that acute diffuse peritonitis accounted for 54% of the cases of septic shock and that large intra-abdominal abscesses with peritonitis were responsible for an additional 12%. Extensive soft tissue infection of the abdominal wall or perineum was another important cause.

On the basis of our experimental work, the following plan of treatment has been evolved and used at the Cincinnati

General Hospital during the past three years and is instituted as soon as a diagnosis of septic shock has been made: 1. Fluids are immediately infused by the intravenous route, particularly normal human plasma or blood, in an attempt to correct any deficiency of the circulating blood volume without overloading the circulation and producing pulmonary edema. 2. Massive doses of antibiotics are administered by the intravenous route. The agents chosen for each case vary, and, in the absence of specific sensitivity data, the selection of the antimicrobial agent necessarily must be made on an empirical basis. Antibiotic-sensitivity data, when available, are helpful for specific selection of the antimicrobial agent. The existence of shock makes the intravenous route advisable and particularly important, not only because of the impairment of absorption from other routes but also because of the urgent need for a rapid chemotherapeutic effect. 3. Levarterenol (Levophed) bitartrate administered intravenously by drip, in a solution of 5% dextrose and water for injection, may be used to restore the blood pressure to a level of 80 mm. Hg or above. This is done in an effort to maintain the various physiological functions, particularly renal, until the infection is brought under control. 4. Oxygen is administered continuously by nasal catheter or tent. 5. The foot of the bed is elevated 12 to 18 inches. 6. An indwelling catheter should be used to measure the hourly urinary output, which is maintained between 25 and 75 cc. per hour by the regulated administration of fluids and levarterenol. 7. Cortisone (Cortisone, Cortogen, Cortone) acetate or hydrocortisone (Cortef, Cortril, Hycortole, Hydrocortone) is probably not indicated unless a blood pressure of 90 mm. Hg or more cannot be restored by the administration of fluids and levarterenol. Under these circumstances, it has been our experience that hydrocortisone has been useful in extending the patient's life until the severe infection could be controlled by intensive antibiotic therapy and any indicated surgical treatment. 8. Timed surgical intervention is recommended, when indicated and feasible.

Previous to the adoption of this therapeutic regimen, the occurrence of circulatory failure in a patient with a severe infection was usually followed by death within a matter of hours. Since its adoption, 36% of the patients with septic shock have been treated successfully at the Cincinnati General Hospital.

Summary

Infection continues to be a major problem in the treatment of patients with wounds of violence. Prophylactic antibacterial therapy has failed to decrease significantly the incidence of infection as a complication of injury, except in the instances of those produced by beta-hemolytic streptococcus and pneumococcus and in penetrating wounds of the abdomen and chest. Nevertheless, prophylactic antimicrobial treatment is recommended, since there are data to indicate that many infections developing within wounds are localized or attenuated by these agents.

On the other hand, antimicrobial treatment has been of considerable value in the control of established infections which complicate wounds, provided use of these agents has been adjunctive to surgical treatment and has been based on certain proved principles which have been discussed.

As a consequence of the misuse of these antibacterial agents, a number of problems have been created, one of which has been an increased incidence of emergent antibiotic-resistant bacterial infections. Such lesions are doubly serious and more difficult to control. It is recommended that more thoughtful and conservative use of antibiotics be adopted in the management of patients with injuries, in an effort to avoid the allergic reactions, secondary or superimposed infections, emergent-resistant infections, and antibiotic toxicity from excessive doses of the broad-spectrum antibiotics. Clinical experience indicates that wound infections are, and will continue to be, a serious problem as long as their prevention and control are dependent primarily on the prophylactic use of antimicrobial agents and not on early and adequate surgery in association with their adjunctive use.

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Control of Suffering In Severe Trauma

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► I HAVE CHOSEN the word "suffering" instead of "pain" because it more accurately describes the problems to be considered here. In recent years it has been found possible and rewarding to deal with subjective responses—symptoms—in a quantitative manner. There is not time now to describe the technical approaches to these problems. In any case, such descriptions are readily available.[1]

The problem of pain is doubtless as ancient as the human race, and, perhaps because it is so old, it seems to have gathered about it more folklore than anything else in medicine. In the present instance, the quantitative approach has made it possible to recognize and dispose of some unfounded traditional statements. This might be called a negative benefit. There are positive ones as well. The necessary validation for the statements to be made can be found in the references already given. It might be well to mention for those who are not familiar with the work of recent years in this field that one can, so to speak, titrate the pain of postoperative wounds of a group with two series of solutions, each series containing different but unknown concentrations of morphine, and, using the approved double-blind technique, find, when the codes are broken, that one has equilibrated 10 mg. of morphine to 10.8 mg., an 8% error. Sound mathematical usage requires that regression lines be calculated for the two curves involved, which adds 2% more, so one can work with a total error of 10%.[2] That is, I submit, about as accurately as one can make objective measurements, such as blood pressure determinations and red blood cell counts, in man.

Reaction Factor

One of the positive benefits of the quantitative approach has been the emergence of factual support for a 65-year-old hypothesis. In 1894, Marshall[3] prepared the way for a crucial assumption first grasped by Strong[4] in 1895. In effect, Strong said that suffering has two major components: First, there is the original sensation, produced, in the case of pain, by stimulation of pain endings by some noxious agent. Second, there is the meaning of this sensation, called the reaction or processing component.[5] Strong must be credited with an important working assumption. As far as one can tell now, this was one of those intuitive, almost clairvoyant, insights, for Strong had no clear factual data to support his assumption. Strong factual support has been obtained for it.[6]

Since the factual supporting data are highly pertinent to our discussion, it will be well to summarize these facts. The assumption can be restated to advantage: The significance of the wound determines the suffering therefrom. Evidence for the existence and importance of the reaction component can be seen in the extraordinary effectiveness of placebos.[7]

Thirty-three per cent of persons with severe pain of pathological origin are satisfactorily relieved by placebos. (What constitutes satisfactory relief is, of course, carefully defined and standardized.)

Only 3% of persons with pain as ordinarily contrived experimentally have such pain relieved by placebos.[8] Thus, placebos seem to be more effective when the stress is great than when it is less.

Even large doses of morphine will not dependably alter the experimental pain threshold as usually produced,[1a] yet a small dose of morphine will completely relieve the pain of a great wound.

Of men severely wounded in battle, but mentally clear, who were not in shock and who had not received morphine or other analgesic at all in many cases and in no case within four hours, only 25% stated, in response to a direct question, that they had enough pain to want anything done about it.[9] Yet civilians with far smaller postoperative wounds have sufficient pain in over 80% of the cases to require medication for it.[10] This is true whether the operation has been for a long-wasting disease, as cup arthroplasty of the hip for degenerative arthritis, or whether it has been performed for the treatment of a fresh fracture. These two groups compared present strong evidence that the significance of the wound determines the suffering therefrom. The soldiers mentioned were chiefly on the Anzio beachhead where the shelling never stopped day or night for months. The war was suddenly over for the person who was wounded. The wound was a ticket to the relative safety of the hospital and a ticket home. The wound was construed as a good thing. With civilians, however, the necessity for surgery is usually considered to be a disaster. It does indeed appear that the significance of the wound—the reaction component—was the crucial factor in the suffering experienced.

I well remember a rainy night on the Anzio beachhead. The blackout canvas of the shock tent was suddenly thrust aside, and three litter bearers carried in a wounded soldier who was screaming to get off the litter. He thought he was lying on his rifle. It was impossible to examine him in his wild state. A modest dose, 120 mg., of amobarbital (Amytal) sodium was given intravenously, after which the patient became quiet and relaxed. He slept but could be easily aroused. He was not anesthetized. It then became possible to undress and examine him. The "rifle" he had been lying on was, in fact, sensation from eight ribs cut in two by a shell fragment. One rib had punctured the diaphragm and a kidney. This striking example was seen by many physicians. The effectiveness of a relatively small dose of barbiturate in handling the pain of some of the severely wounded was subsequently widely confirmed. It is probable that barbiturates are most effective when injuries are associated with great fear and anxiety. Whether this explanation is correct is beside the immediate point: The foregoing types of information are evidence for the existence and importance of the reaction component. Indeed, it would be next to impossible to explain these observations on any other basis. It is perhaps not too strong a statement to say that they prove the existence and importance of the reaction factor.

Shock and Suffering

It is, of course, not possible to deal very long with severe trauma without encountering the problem of wound shock. In this connection I should like to make several points.

Overusage of Analgesic Agents.—In the minds of too many physicians, the presence of a severe injury or burn is all the indication needed for the injection of a large dose of morphine or other analgesic agent. This may not only be unnecessary but can be, in fact, a dangerous error. Let us consider several common situations. First, as I have indicated previously, there is no direct relationship between the extent of the wound and the suffering experienced from it. (You will recall that 75% of the men wounded in battle and not in shock had no pain or so little they did not want anything done about it, whereas civilians with the comparatively small wounds of surgery required pain relief more than three times as often.) Second, it is curious that so many physicians have overlooked the fact that wounded soldiers in shock rarely complain of pain. I suppose this has been overlooked owing to the almost universal compulsion to give a large dose of morphine first to a wounded man and ask questions later. This procedure results from failure to understand that there

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is no direct relationship of extent of wound and suffering experienced.

There are three principal reasons why this wrong assumption may be dangerous to the point of folly. 1. The man in shock has probably lost much blood; such patients are exquisitely sensitive to the depressant effects of morphine. 2. The man in shock may have a pneumothorax, and even small doses of morphine can kill and have killed such men. 3. The peripheral circulation is hardly active in shock, so that absorption from subcutaneous or intramuscular deposits will occur exceedingly slowly or not at all.[11] In case the patient is one of the rather unusual ones who truly have pain, no pain relief will occur, and a second or even a third dose may be given, with the consequence that, when the man is resuscitated and warmed up, with restoration of his peripheral circulation, all of the several deposits of morphine will be absorbed at once, and profound morphine poisoning, even death, can occur.[12] This is called delayed morphine poisoning and is inexcusable. If the man in shock truly has pain, one-third of the usual dose of morphine should be administered intravenously. Delayed absorption doubtless lies back of the tradition of giving large doses of morphine to those with extensive burns, chilled as such persons are by the fireman's hose and sometimes in shock. It can easily be seen why the unsound practice of giving large doses of morphine to the burned has grown up, since the morphine is unlikely to be effective unless given intravenously. 4. Less important than the aforementioned points, but still worth taking into account, is the fact that morphine can change a positive fluid balance of the wounded into a negative one through increased sweating and the induction of vomiting, with fluid loss.

Thirst.—As indicated previously, wound pain in the man in shock may not be present. There is, however, a common cause of great suffering in the person in shock, and this is thirst. It is remarkable how neglected this important symptom often is. Even in warfare severe dehydration is rather uncommon in the newly wounded, and it is not present in civilians as a rule; therefore, complaints of thirst are an ominous warning of deteriorating condition. It appears to be directly related to a sharply decreasing circulating blood volume. It is doubtful if mouth washes have any alleviating effect. The treatment is restoration of blood volume.

Mechanical Factors.—The pain of the wounded can often be relieved by improved splinting of the wound. Fractures of the leg result in great distal swelling. The slitting of a tight shoe will release the swollen foot and often lessen, sometimes relieve, the pain of a fractured femur.

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Early Management of Fractures

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► THE EARLY MANAGEMENT of fractures embraces both the temporary emergency management and the early definitive management of both open and closed fractures. The temporary emergency management is nothing more than the emergency splinting for transportation to and within the hospital. This is a facet of management of fractures lacking in color, appeal, and, all too often, professional interest. However, it remains an exceedingly important, albeit a frequently neglected, part of early management. Fractures of long bones, particularly those of the lower extremities, must be splinted at the first opportunity if the best interests of the patient are to be served.

Emergency Splinting

The significance of effective emergency splinting must not be underevaluated. It prevents further damage to soft parts by sharp fragments. In so doing, it may prevent the catastrophe of laceration of a major blood vessel or a peripheral nerve or compounding of a closed fracture. It minimizes pain, contributes to resuscitation from shock or helps to prevent it, and makes the casualty transportable with increased safety. Indeed, the ultimate results of the most expert definitive management may be wholly or in part predetermined by the quality of emergency medical care rendered at the scene of the accident.

Emergency splinting for transportation is preferably applied at the scene of the accident by well-trained ambulance personnel or law-enforcement personnel. When a patient with a broken extremity arrives without a splint at an emergency room, however, the obligation of the physician to provide effective splinting immediately, before the patient is transported to the x-ray room or to his bed, is increased rather than diminished. Emergency splinting should be provided by the first person in attendance having the capability, whether professional or subprofessional.

If emergency splinting were a difficult procedure, its omission might occasionally be excused. It is, however, a simple, easy procedure. Emergency splinting for fractures of the long bones of the upper extremity is particularly easy. Almost any kind of short board splint or even a magazine wrapped around the part will provide adequate splinting for fractures of the forearm. Fractures of the arm, including the shoulder, require only the support of the forearm in a sling and the band-

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aging of the entire extremity to the chest wall. Patients with fractures of the long bones of the upper extremity are usually more comfortable when they are transported in the sitting rather than the recumbent position.

Emergency splinting of fractures of the long bones of the lower extremity is a little more difficult and requires more material, but it remains a relatively easy procedure. For fractures of the femoral shaft, fixed-traction splinting in a Thomas or half-ring leg splint, with a traction hitch being used about the ankle, remains the preferable method. Coaptation splinting with padded long boards, however, is also a highly effective method that is most acceptable. Such material can usually be obtained with little effort. For fractures of the femoral shaft, a long board should extend from the chest wall down the outer side of the extremity. Other short boards are placed along the medial and posterior surfaces of the injured extremity. All boards are bandaged firmly to the extremity, and the long board is also bandaged to the trunk.

For fractures of the bones of the leg, coaptation splinting, with board splints or other comparable material, as previously described, is preferable to fixed-traction splinting. Of course, the lateral board need extend only to the upper thigh. A pillow bandaged firmly about the leg, with or without lateral boards, will provide effective transportation splinting.

In open fractures, only a sterile or clean dressing of the wound is indicated. Protruding fragments should not be pulled back beneath the skin but, rather, should be covered with a dressing and left protruding until the patient reaches facilities for surgery.

Definitive Management

The first step in the definitive management of both open and closed fractures is a choice of method of management by the treating physician. The methods of management of fractures may be classified as (1) closed reduction, if necessary, and immobilization; (2) continuous traction, usually skeletal; (3) open reduction, usually with internal fixation; (4) external skeletal fixation, which includes multiple pins incorporated in a plaster cast; and (5) no immobilization or, at the most, only a bandage and sling. Each of the many varieties of treatment for fractures will fall within this classification. The physician must select and institute promptly the method likely to lead to the optimal result under the circumstances in that particular patient. The choice of method necessarily will depend, in part, on the skill and experience of the surgeon and the facilities and equipment available to him. He must make certain that the method selected is effective and adequate, otherwise it must be abandoned in favor of another. Possibly the most common error in the treatment of fractures is to blindly and stubbornly adhere to the method first selected (even though it is not effective) rather than to recognize that another method must be instituted.

Most fractures are best managed by one, and only one, of the five methods just described. Whereas most are best handled by method 1 (closed reduction and a cast), with many fractures it would be doomed to failure. Some fractures should be recognized immediately as requiring the use of method 2 (continuous traction); a great many others, method 3 (the open-operative method); an occasional one, method 4 (multiple-pin fixation in plaster); and in a fair number, method 5 (the non-immobilization method).

As examples, closed reduction in a plaster cast is indicated in practically every undisplaced fracture, most displaced fractures about the wrist, some displaced fractures about the ankle, all fractures of the shaft of long bones in children, except those in the femur, and stable fractures of the tibial shaft in adults. A stable fracture of the tibial shaft is one with a contour usually transverse or near-transverse, which, after reduction, will not slip or override while in a plaster cast. Continuous traction is indicated in most fractures of the femoral shaft in children and in those fractures in adults too comminuted for intramedullary fixation, for some supracondylar fractures of the humerus in children as either Dunlop's skin traction or skeletal traction through the olecranon, and, in the form of a hanging cast, for most fractures of the shaft of the humerus. The open-operative method is immediately indicated for fractures of the neck and trochanteric region of the femur, for fractures of the shaft of the femur if not too comminuted for intramedullary nailing, for separated fractures of the patella and the olecranon, for most unstable fractures of the tibia, for many fracture-dislocations of the ankle, and for selected fractures about the elbow in both adults and children. Occasionally, multiple-pin fixation in a plaster cast will be advantageous for comminuted fractures of both bones of the leg. No immobilization and early active use are indicated in impacted fractures of the surgical neck of the humerus, many undisplaced fractures of metatarsals, and many fractures of the distal phalanges of the fingers.

The timing for the application of each of these methods of management may be exceedingly important. Closed reduction should be carried out as soon after injury as possible. The closed reduction of fractures is more likely to be successful if it is carried out while the hematoma is still liquid and before excessive swelling has developed. The bone fragments may be more easily palpated and manipulated and the plaster cast applied before excessive swelling takes place. By contrast, if efforts at closed reduction are delayed, the soft parts surrounding the fracture become infiltrated with the products of inflammation and are made inelastic and waterlogged, so that closed reduction becomes increasingly difficult.

The closed reduction of displaced fractures should be considered an emergency except in those situations in which general anesthesia is necessary but is contraindicated at the time. Such a situation can easily present itself when the patient is known to have a full stomach. Preferably, a general anesthetic is not administered to a patient who has eaten during the previous eight hours. For practical purposes, a general anesthetic should never be administered to a child for the closed reduction of a fracture unless the child's stomach is known to be empty because the hazard of aspiration of vomitus, with its dire consequences, is too great. In some instances, such as in a displaced supracondylar fracture of the humerus in a child, when the presence of a full stomach precludes administration of general anesthesia, the fracture may require continuous traction, perhaps in the form of Dunlop's traction, to be selected as the desirable method of management in preference to closed reduction and immobilization.

The institution of other methods of management is not so urgent, but the sooner the fracture is reduced the better for the fracture and the patient. The sooner continuous traction is initiated, the better the chances for reduction. Open reduction is often performed as an emergency, before excessive swelling takes place. For example, in fractures about joints such as fracture-dislocations of the ankle, prompt open reduction as an emergency is usually advisable, barring contraindications. To delay operation in this injury only permits increased swelling, which, in itself, can further delay the surgery beyond the time when the operation may be carried out with the anticipation of the optimal result. When incisions are made through badly swollen tissue, ischemia and necrosis of sutured wound margins may follow. In fractures of the hip in aged patients, the best interest of the patient may be served by prompt operative fixation of the fractures. The severe, immobilizing pain of the fracture will be relieved; the patient may be turned in bed and gotten into a chair promptly, thereby minimizing the danger of pulmonary complications and decubitus ulcers. As a general rule, fractures should be reduced as promptly as possible by whatever method the physician considers is indicated, unless there are concurrent injuries or diseases which demand that definitive reduction of the fracture be postponed.

Early and prompt institution of the indicated method of management is advisable and often mandatory for the best treatment of a fracture. Delays which are avoidable only complicate the problem and predispose to complications and inferior results.

Open Fractures

Open fractures demand prompt definitive management as surgical emergencies. They deserve investigation, appraisal,

and treatment in a fully equipped operating room. General anesthesia is indicated, with few exceptions. Stomach lavage to remove gastric contents may be advisable to permit administration of general anesthesia, with less risk of vomiting and aspiration and their dire consequences. The fractured part should be surgically cleaned, prepared, and draped and the wound examined thoroughly. The indicated surgical procedure is determined by the amount of damaged tissue probably remaining in the wound and the degree of contamination.

Hard and fast rules as to the extent of wound surgery in open fractures cannot be made. The situation varies with the magnitude and type of wound. The objectives of surgery in every wound, however, are the same: (1) to make it as free as possible of those things which predispose to infection—that is, dirt, debris, dead and devitalized tissue, and massive blood clot; (2) to determine whether the wound should remain open or be sutured; and (3) to determine how the fracture should be managed.

In the technique of wound débridement, exposure of the depths of the wound must be adequate. As a rule, the wound must be extended. The incision through skin and fascia must be of adequate length to give free access to devitalized muscle, since its excision is a major objective of wound débridement. Healthy muscle is not discolored, bleeds freely and contracts when pinched; muscle which does not meet these requirements should be excised. Foreign bodies and all dirt and debris should be removed. For thorough irrigation of the wound, saline solution is a valuable cleansing agent. Bleeding vessels should be ligated. Small fragments of bone completely devoid of soft tissue attachment should be removed, but bone which has some muscular or fascial attachment should be left in place as it is usually viable.

After débridement of the wound has been completed (and, perhaps, the fracture reduced), a decision must be made whether to close the wound or to leave it open. When surgery has been performed within the first six hours after injury, when cleansing and débridement have been thorough, and when closure appears to be surgically feasible without excessive tension, closure of the wound by suture is usually indicated. On the other hand, if the surgeon cannot be reasonably certain that the wound has been rid of the pabulum of sepsis or if closure by suture would produce excessive tension on the sutured margins of the wound, either immediately or after postoperative swelling has taken place, then, an open wound is preferable. The error should be made on the side of leaving the wound open because delayed closure may be carried out with increased safety several days later. It seems reasonable to state that too many primary closures over open fractures are attempted, and the advantages of an open wound, with delayed closure, are too often overlooked.

Insofar as the fracture is concerned, the same methods of management, in general, are applicable to open or closed fractures. In the former, however, the question of using internal fixation at the time of wound débridement often arises. Internal fixation of open fractures is a calculated risk which requires expert judgment, but the method is often indicated. Certainly, if internal fixation is to be used, the time-lag after injury should be short; the wound must have been débrided well; residual dead space in the wound must be at a minimum; and closure of the margins of the wound by suture must be feasible. If these requirements are not met, internal fixation is probably too hazardous. It would be preferable to use some other method of management and to direct all efforts toward obtaining wound healing, after which, open reduction and internal fixation, if indicated, may be carried out through an intact skin-envelope.

Summary

Open fractures demand prompt definitive management as emergencies. The objective of management of the wound is to prevent infection. Unless the surgeon can be sure that the depths of the wound have not been contaminated and that all tissue within the wound is viable, enlargement of the wound and a thorough débridement are indicated. The choice of the method of management for the fracture requires expert judgment. The fracture must not be ignored, and it must be reduced. Reduction of the fracture minimizes dead space and actually predisposes to wound healing, without infection. A septic fracture is usually an unreduced fracture. Because maintenance of reduction of the fracture and immobilization of the fragments are important deterrents to infection, internal fixation often is indicated as a part of wound management.

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Active and Passive Antitetanus Immunization

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► THE COMPLETE EFFECTIVENESS against tetanus of the active immunization of persons, as produced by a series of tetanus toxoid injections, was thoroughly established by the experience of the armed forces of the United States during World War II. The sole qualification which must be attached to this statement, however, is of the utmost importance today to the practicing physican who must treat an acutely injured patient. In order to take advantage of this immunity, the physician must be certain that such a patient has previously been given an adequate course of toxoid injections. On the other hand, the protective value of tetanus antitoxin when adequate dosage is used has also been established by experience. The latter constitutes prophylaxis by means of passive immunization, but the method involves all the disadvantages and dangers of the administration of foreign protein. It is probably fair to say that there are few physicians who treat patients for injuries who would not be gladdened to learn of a safe substitute for tetanus antitoxin. If tetanus were a contagious disease comparable to smallpox, it is likely that public opinion would make active immunization compulsory for all persons. Only by a mass immunization program can the annual death toll from tetanus be wiped out. Despite the active efforts of many physicians to bring about mass immunization, they have not been successful; for the present, at least, the antitetanus measures must be suited to the person undergoing treatment.

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Review of Causative Mechanism

In order to better comprehend the rationale of present methods, it seems worthwhile to review the facts. The clinical manifestations of tetanus result from the effects on the peripheral and central nervous system of the powerful toxin produced by the living bacillus, Clostridium tetani. This organism, a spore-bearing, strict anaerobe, is distributed widely throughout the world. It is found commonly in the feces of barnyard animals and birds (including pigeons), and it can also be found in human feces, although to a lesser extent. Little or no inflammation attends the growth of the bacteria in human tissues, and it appears that even the most trivial

injury to living tissues may result in enough local damage so that the spores can develop into bacilli, which then begin to manufacture toxin. Tetanus toxin reaches the central nervous system either by way of a peripheral nerve trunk or through the bloodstream and has been demonstrated to be present in the blood 12 to 24 hours before the symptoms of tetanus become apparent. Tetanus toxin becomes fixed in the tissues of the central nervous system, after which such toxin can no longer be inactivated by antitoxin.

Prophylaxis

From these facts, it may be concluded that there could be, in theory, four entirely different methods of preventing clinical tetanus. The first and probably the best of these is the prevention of injury. The second method of prevention of tetanus is the proper treatment of the wound in order that anaerobic growth may not take place. The third theoretical prophylactic measure would be the use of agents, either chemotherapeutic or antibiotic, which prevent the growth and development of the bacilli. The fourth prophylactic method is, of course, the use of some means to neutralize or inactivate tetanus toxin. The latter measure is the subject of this discourse. Accordingly, it should be emphasized that immunization against tetanus, whether active or passive, is directed against tetanus toxin and not against the micro-organisms. If one remembers this point, it is easier to understand why immunization might fail to protect, since the bacilli might continue to grow and to produce toxin beyond the capacity of the immunizing substance to inactivate it.

It is of passing interest to mention that recovery from the disease does not produce immunity. There have been many reports of repeated attacks of tetanus in persons, and studies of the blood taken from patients who recovered did not show an antitoxin titer after an interval sufficient to permit excretion of the antitoxin given the patient therapeutically. The explanation for this probably lies in the fact that the amount of tetanus toxin which is lethal to a man is too small an amount to produce an immunity.

Passive Immunization

Tetanus antitoxin is prepared by injecting animals, notably the horse, with sublethal doses of tetanus toxin prepared from broth cultures of Cl. tetani or with tetanus toxoid. Tetanus antitoxin is then prepared from the blood serum of the immunized animal. One unit of tetanus antitoxin will protect a 350-Gm. guinea pig against about 1,000 lethal doses of tetanus toxin. It should be realized that it is not possible to state what constitutes a protective level of antitoxin in the human being because, obviously, the amount of toxin being produced by the micro-organisms is the deciding factor. It is intriguing to consider the complacency with which most physicians have, until now, administered 1,500 units of tetanus antitoxin, believing that the patient was thus protected. A single dose of 1,500 units of tetanus antitoxin, as commercially obtainable, will, if given intramuscularly, produce a gradually rising titer of antitoxin in the circulating blood which, by the fourth or fifth day, reaches a level of 0.1 unit of antitoxin per milliliter of serum. This level is maintained until about the 10th or 11th day when it begins to fall. By the end of the third week, there will usually be no demonstrable titer in the blood.

Not long ago, the records of all of the patients treated for tetanus in the general hospitals of Baltimore during a 25-year period were reviewed. Tetanus is not extremely common in Baltimore, as only seven or eight patients per year are treated. Records were found of 25 patients who had been given 1,500 units of tetanus antitoxin at the time of treatment of their original injury but in whom the symptoms of tetanus appeared, nevertheless. Of this group, 13 died of tetanus: thus, it would seem that these patients, at least, were not afforded adequate protection. It has been shown that an initial administration of comparable amounts of tetanus antitoxin to laboratory animals is not protective when lethal doses of live spores are introduced. It is the feeling of the majority of physicians working in this field today than any injured person who really needs tetanus antitoxin probably needs a larger dose than 1,500 units.

It has been stated that the commercially available tetanus antitoxin is, for the most part, prepared from the serum of the horse. Antitoxin prepared from bovine serum, however, is also available. A third and probably safer source of tetanus antitoxin is that obtainable from the blood of immunized persons. This has not been made commercially available as yet but probably should be because the complications of the administration of horse serum are disabling and dangerous. It behooves any physician who treats an injured person to consider carefully whether, in the individual circumstances, the danger to life is greater from tetanus or from the effects of the horse serum. Physicians familiar with the emergency rooms of large city hospitals have the uncomfortable impression that more and more of the population appear to be hypersensitive to horse protein. It is not necessary for a person to have had a previous injection of horse serum in order to develop hypersensitivity. This state can be acquired from exposure to horses or even, according to some authorities, from eating horse meat. A variety of consequences follows the injection of the horse serum. The most disastrous, of course, is the rather immediate occurrence of anaphylaxis and death. The more common complication is that of urticaria and serum sickness. I have not seen an accurate account of the human discomfort, disability, and mortality resulting from tetanus antitoxin, but there have been reports of damage to the central nervous system, including paraplegia, hemiplegia, and encephalitic manifestations of a lasting nature. As is well known to all physicians, any of these complications may occur, despite careful preliminary tests for sensitivity.

Active Immunization

Active immunization against tetanus was introduced by Ramon in 1925. As has already been mentioned, the biological perfection of this method was demonstrated during World War II, during which there was almost no occurrence of tetanus among the personnel of the armed forces of the United States. There was, however, a high incidence of this dread complication of injury among the troops of our enemies who were not actively immunized, especially in the islands of the Pacific. Although the authorities of the United States are not in full accord as to whether alum-precipitated toxoid or the fluid toxoid constitutes the most suitable antigen for the production of active immunity, it is, nevertheless, certain that two or three monthly injections of either preparation, followed some months later by a booster dose, will produce a lasting active immunity against tetanus toxin. It has been shown that this immunity persists for more than 10 years; high titers of antitoxin in the circulating blood are promptly recallable by a booster injection of toxoid. Hypersensitivity to tetanus toxoid is rare, although it does occur. Active immunization in such hypersensitive persons can be accomplished by intracutaneous injection of small amounts of the toxoid, with minimal risk. It must be pointed out, however, that there is an interval of at least 14 days between the first injection of toxoid and the appearance of significant amounts of antitoxin in the circulating bloodstream. On the other hand, when the person has received a previous course of toxoid injections, a booster dose produces a prompt recall, and the level of antitoxin is demonstrable within three or four days. Within seven days after such a booster dose in an actively immunized person, the level of antitoxin in the circulating blood will be quite high. Furthermore, this level remains for more than a year, far beyond the brief, temporary level produced by passive immunization.

The point must be again emphasized: Whereas active immunization with tetanus toxoid constitutes the best possible prophylaxis against tetanus, this method is of no use whatsoever in the treatment of a patient acutely injured unless that patient has already received his full immunizing course at some previous time. Currently under study are methods which, it is hoped, will result in the rapid production of active immunity; the certainty of these methods has not yet been established.

Comment

It is of interest to point out that there is a large, random experiment going on in the United States at the present time. It is well known that tetanus commonly complicates trivial wounds for which the patient does not seek medical aid. As a result, these patients first appear at a physician's office with full-blown tetanus. Furthermore, there is a growing reservoir in our population of persons who have had a basic course of active immunization but who have not had routine booster doses. Since 1950, many children in the United States have received tetanus toxoid, together with diphtheria toxoid, in infancy. There are also more than 15,000,000 persons in the nation who were immunized during their service in World War II, many of whom have probably had no booster dose subsequently. It should be possible in the next 5 to 10 years to gather a large body of information concerning the experience of these children and former armed services personnel for contrast with that of the rest of the population who are not immunized. This information will serve to prove whether immunity to tetanus toxin is of a lasting nature and whether booster doses are necessary at the time of injury.

Recent experimental work in the laboratory has shown that, if the course of therapy is begun at the time of injury, penicillin and broad-spectrum antibiotic agents such as tetracycline (Achromycin, Panmycin, Polycycline, Steclin, Tetracyn) hydrochloride are more protective against tetanus than are ordinary doses of antitoxin. These antibiotic agents appear able to prevent sporulation and growth of the bacilli, and, thus, no toxin is produced. There are two obvious points to be made concerning the use of antibiotics in this connection. The first and most important of these is that antibiotic agents do not neutralize tetanus toxin and, therefore, cannot be relied on to protect a patient in whom toxin is already being produced. The second point concerns the treatment of a patient who has tetanus. Antibiotic agents are quite useful in controlling the growth of the tetanus bacillus and, therefore, in reducing and possibly eliminating the source of the toxin when the source cannot be controlled by direct surgical means. If antibiotic therapy is used for prophylaxis, full dosage should be given for five to seven days.

There is, at the present time, a renewed interest in the subject of tetanus prophylaxis. The interest is due, in part, to the rather frequent occurrence of this complication of injury among patients in the southern states and to a growing abhorrence of the morbidity and mortality which are the consequences of widespread, routine use of tetanus antitoxin. Undeniably, the ideal solution to the problem is mass immunization of the population. Numerous county and state medical societies are already actively developing such programs. One of the unsolved problems of an immunization program concerns the identification of persons who have been immunized. It would seem to me that a good method for handling this problem would be to keep indexed immunization records of the population in state or county health departments so that a phone call or a telegram could produce the desired information promptly.

Summary and Conclusions

Until the day arrives when all of us have had active immunization to tetanus, however, each physician who treats injured patients must be ready to individualize the prophylactic measures against tetanus. The following steps are suggested as a guide: 1. Careful selection of patients for antitetanus measures is necessary. 2. Thorough cleansing and débridement of the wound must be done, in order to minimize the conditions favorable to anaerobic growth. At times, in large wounds with crushed tissues, this may involve leaving the wound open. 3. If the patient has been previously actively immunized (with a full course of tetanus toxoid), he should be given 0.5 cc. of fluid toxoid intramuscularly. 4. If the patient has not been previously immunized, he should be tested for sensitivity to horse serum, after careful questioning about such matters as previous injection or other allergic manifestations. Sensitivity testing is a medical responsibility and should not be delegated to nurses or other personnel. Both conjunctival and intracutaneous tests are useful. If the sensitivity tests are negative and if the physician has determined that the wound is one which may be complicated by tetanus, then tetanus antitoxin should be given; 5,000 units constitutes an adequate dose. The previous standard of 1,500 units should not be relied on as adequate. 5. If the patient has previously had antitoxin in horse serum or is sensitive to horse serum, bovine serum should be tried. There is still some controversy as to the virtues of administering antitoxin to a hypersensitive person. Under such circumstances, severe serum sickness is likely, and there is some doubt as to the duration of the passive immunity. If antitoxin is given to a hypersensitive person, it should be given carefully in graduated amounts and with the added precaution of having available epinephrine, antihistaminic drugs, cortisone (Cortisone, Cortogen, Cortone) acetate, and the equipment needed for the intratracheal administration of oxygen. Although this is generally called "desensitization," it does not render the patient insensitive to horse serum. 6. The use of penicillin or broad-spectrum antibiotics is indicated in persons who are extremely hypersensitive to horse and bovine serums and who are treated within an hour or two after injury. Full dosage of the agent should be given for five to seven days. 7. The treatment of an injury is probably an excellent time to begin the immunizing course of tetanus toxoid in those who have not previously been immunized. If this is done, however, care must be taken not to mix the toxoid and antitoxin in the same syringe nor to inject them in the same extremity, because one will inactivate the other. Separate syringes and needles and separate extremities should be used for each agent. 8. All physicians should take every opportunity to extend as widely as possible the benefits conferred by active immunization against tetanus.

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POSITIONS

in hospital pharmacy

PERSONNEL PLACEMENT SERVICE

The Personnel Placement Service is operated without charge for the benefit of hospitals and pharmacist members of the American Pharmaceutical Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. The ultimate purpose is the improvement of pharmaceutical services in hospitals, by more adequately fulfilling hospital pharmacy personnel needs and by locating positions which provide challenging opportunities for pharmacists who have indicated an interest in a hospital career.

By participating in the service, the hospital indicates a desire to achieve a pharmaceutical service which meets the *Minimum Standard for Pharmacies in Hospitals.* A description of the position should be submitted to the Division of Hospital Pharmacy on the forms provided. The hospital will receive applications directly from the applicant. The hospital agrees to reply to each application received and to notify the Division of Hospital Pharmacy when the position is filled.

The pharmacist, by participating, agrees to submit a Personnel Placement Service Information Form to the Division of Hospital Pharmacy. The applicant will then be notified of openings listed with the Service as they become available and can negotiate directly with the hospital if he is interested. It is agreed that the Division of Hospital Pharmacy will be notified as soon as a position is accepted.

A listing of positions open and wanted will be made regularly in the AMERICAN JOURNAL OF HOSPITAL PHARMACY without charge. Neither the name of the hospital offering the position nor the name of the applicant will be listed, except by code. All inquiries should be directed as shown above, including the code number.

Address all inquiries to

Division of Hospital Pharmacy
2215 Constitution Avenue, N. W.
Washington, 7, D. C.

positions open

CHIEF PHARMACIST—80 bed general hospital located in Florida. Pharmacist will have charge of all purchasing and dispensing. Must be eligible for licensure in Florida. Forty-eight hour week, vacation and insurance. PO-229

ASST. CHIEF PHARMACIST—160 bed general hospital. Will be responsible for pharmacy dept. in absence of chief pharmacist. Must be eligible for licensure in Illinois. Male or female. Forty hour week, vacation. PO-228

ASST. CHIEF PHARMACIST—400 bed general hospital. Must be eligible for licensure in Virginia. Forty-four hour week, vacation, liberal benefits. PO-227

STAFF PHARMACIST—550 bed teaching hospital located in Virginia. No experience necessary. Female preferred. Forty hour week, vacation, liberal benefits. PO-226

CHIEF PHARMACIST—General hospital located in West Virginia. Pharmacist will be under direct supervision of the administrator, filling prescriptions and allied duties; planning; organizing; and directing pharmacy and central sterile supply in accordance with established policies. B. S. required. Forty hour week, liberal benefits. PO-225

CHIEF PHARMACIST—100 bed general hospital located in Ohio. Applicant must have organizational ability and will assume administrative responsibilities of the dept. Must be registered. PO-224

ASST. CHIEF PHARMACIST—90 bed general hospital located in Colorado. Duties include compounding and dispensing medications and assuming responsibility of pharmacy dept. in chief pharmacist's absence. Must be eligible for licensure in Colorado. Forty hour week, vacation, sick leave and hospitalization. PO-223

STAFF PHARMACIST—400 bed general medical surgical and teaching hospital. Duties include inpatient and outpatient dispensing, manufacturing bulk liquids, ointments, galenicals, small and large volume parenterals and surgical fluids. Will also assist in supervision of students and hospital pharmacy interns. Prefers applicant with hospital pharmacy experience and/or hospital pharmacy internship with some manufacturing experience. Male preferred under forty years of age. Forty hour week, vacation and educational benefits. PO-222

CHIEF PHARMACIST—Psychiatric hospital located in Ohio. Must be registered in Ohio, forty hour week, vacation and retirement benefits. PO-221

STAFF PHARMACIST—400 bed general hospital located in Texas. Duties include dispensing, etc. Applicant must have B.S. and be eligible for registration in Texas. Forty hour week, two weeks vacation. Write: Pharmacy Department, Harris Hospital, Fort Worth, Texas. PO-219

ASST. CHIEF PHARMACIST—200 bed general hospital located in Connecticut. Duties include filling of medication orders, preparing stock drugs and filling inpatient and outpatient prescriptions. Forty hour week, two weeks vacation and sick leave. PO-218

CHIEF PHARMACIST—260 bed general hospital located in Oklahoma. Duties include planning and organizing policies of dept., preparing and dispensing medications. Prefer applicant with supervisory experience between 25-40 years of age. Forty hour week, vacation, sick days, group hospitalization and pension program. PO-217

ASST. CHIEF PHARMACIST—400 bed hospital. Duties include supervision of general dispensing pharmacy. Prefers applicant who has served an internship. Ohio registration required. Forty hour week, vacation, retirement program and educational opportunities. PO-216

STAFF PHARMACIST—350 bed general hospital. Duties will chiefly consist of dispensing and some manufacturing. Possibility of teaching pharmacology subjects to student nurses. Qualifications: Male, 25-30 years of age, service obligation completed, B. S. and Ohio registration. Vacation, holidays and sick leave. PO-215

STAFF PHARMACIST—188 bed general hospital. Duties include filling patient drug orders and outpatient prescriptions, and assisting chief pharmacist. California registration desired. Forty to forty-eight hour week, vacation, sick leave and group insurance. PO-214

ASST. CHIEF PHARMACIST—380 bed general hospital located in Colorado. Duties include compounding, dispensing, maintaining

stock of pharmaceuticals, and furnishing information concerning medications to physicians, interns, and nurses. Responsible for operation of pharmacy department in absence of chief pharmacist. Vacation, holidays and sick leave. PO-213

CHIEF PHARMACIST—190 bed community hospital located in Virginia. Applicant must have administrative ability as well as organizational ability Must be interested in teaching. Close relationship with medical and nursing staff of the hospital. Forty hour week, vacation, sick leave and retirement plan. PO-211

ASST. CHIEF PHARMACIST—220 bed general hospital. Will be in charge of pharmacy in chief pharmacist's absence. Qualifications: female, B. S., experience in pharmacy administration, licensed in Pennsylvania. Forty hour week, vacation, progressive personnel policy. PO-209

ASST. CHIEF PHARMACIST—500 bed general childrens hospital located in Iowa. Will assist chief pharmacist and will be responsible for the operation of the pharmacy dept. in the absence of the chief pharmacist. Forty hour week, vacation, sick leave and holidays. PO-205

ASST. CHIEF PHARMACIST—238 bed general hospital located in Michigan. Duties include dispensing, controlling pharmacy divisions on nursing units, and assuming responsibility of pharmacy in the absence of chief pharmacist. Forty hour week, vacation, holidays, and sick leave. PO-204

ASST. CHIEF PHARMACIST—204 bed hospital. Duties include dispensing, receiving, and labeling drugs, etc.; furnishing information to physicians and nurses; teaching student nurses; and being responsible as an assistant department head in administrative and other related duties. Forty hour week, vacation, insurance, and sick leave. Must be eligible for registration in Illinois. PO-203

CHIEF PHARMACIST—104 bed general hospital. Direct pharmacy with the help of full-time registered nurses and assist in the purchase of medical surgical supplies. Forty hour week, vacation, and sick leave. Located in a university town in Illinois. PO-202

STAFF PHARMACIST—280 bed general hospital. Intern and resident program, school of nursing and school of medical technology. Building program to include new pharmacy facilities. Must have B. S. in Pharmacy. Michigan registration required or be eligible for licensure. Recent graduate acceptable. Forty hour week, vacation, insurance, pension plan, holidays, and sick leave. PO-199

CHIEF PHARMACIST—300 bed hospital located in Virginia. Pharmacist will have responsibility of organizing dept., purchasing initial stocks, planning policies and procedures, establishing formulary, and serving on Pharmacy and Therapeutics Committee. Forty hour week, vacation, and sick leave. PO-195

STAFF PHARMACIST—790 bed hospital. Duties include handling and filling of inpatient and outpatient departmental orders, outpatient prescriptions and bulk manufacturing. Must be registered or eligible for registration in Ohio. Male preferred. Forty hour week, vacation, holidays, and pension plan. PO-194

ASST. CHIEF PHARMACIST—225 bed general hospital in Hawaii. Assist chief pharmacist; charge of dept. in chief pharmacist's absence. Must be eligible for licensure in Hawaii. Forty hour week, vacation, holidays, annual sick leave, insurance and retirement plans. PO-191

CHIEF PHARMACIST—2300 bed mental hospital. Pharmacist will have complete charge of pharmacy, drug orders, stocking, dispensing, compounding, necessary records, and other pharmacy duties. Must be licensed in Ohio. Forty hour week, vacation, holidays, insurance, retirement plan, and sick leave benefits. PO-189

STAFF PHARMACIST—325 bed general hospital located in Pennsylvania. Duties include filling requisitions from the various nursing stations for floor drugs and completing specific prescriptions to patients. Forty hour week, vacation, and group hospitalization. PO-186

STAFF PHARMACIST—400 bed general hospital located in Michigan. Excellent opportunity in an expanding pharmacy program. Liberal benefits. PO-185

CHIEF PHARMACIST—312 bed nonprofit community hospital. Male or female. Must be qualified and eligible for licensure in Virginia. Forty to forty-four hour week, vacation, and insurance plans. PO-181

CHIEF PHARMACIST—264 bed general hospital located in Texas. Plans and directs pharmacy policies, compounds and dispenses medicines, purchases supplies and materials, maintains records, and prepares periodical reports. Must be eligible for or have M. S. Degree. Forty hour week, vacation, retirement, sick leave and insurance plans. PO-177

STAFF PHARMACIST—290 bed general medical and surgical city hospital. Duties include compounding, dispensing, manufacturing, and assisting in the purchasing of supplies. Prepares reports and maintains records. Furnishes information concerning medications to physicians and nurses. In absence of associate pharmacist will assist with special duties as assigned by chief pharmacist. Male or female between 23-45 years of age. Ohio registration required. Hospital pharmacy internship preferable. Forty hour week, vacation, sick leave, retirement plan, credit union, holidays and insurance. PO-170

STAFF PHARMACIST—200 bed general hospital. Duties include compounding, dispensing, and manufacturing. Applicant must have B. S. in Pharmacy and be registered in Connecticut. Recent Graduate acceptable. Forty-four hour week, vacation, pension plan, and hospitalization. PO-168

STAFF PHARMACIST—100 bed general hospital located in Texas. Assume personal responsibility for accurate filling of prescriptions and supplies, assist in inspecting drugs in nursing stations, replace stock taken from night emergency container, inspect and refill ophthalmic solution trays from operating room, emergency room, and central supply. Female preferred. Must be registered or eligible for registration in Texas. Forty hour week, vacation, holidays, and sick leave. PO-164

ASST. CHIEF PHARMACIST—280 bed general hospital. Duties include filling prescriptions and medication orders from various units, supervise pharmacy clerks, assume administrative responsibility when chief pharmacist is absent. Forty-four hour week, sick leave, and holidays. Must be registered in Illinois. PO-161

CHIEF PHARMACIST—103 bed general hospital. Purchasing, receiving and issuing of pharmacy supplies. Taking inventory once a year. Filling out various reports necessary to operation of dept., etc. Must be registered in Washington State. Forty hour week, vacation, holidays, sick leave, and insurance. PO-158

STAFF PHARMACISTS—Unique, new 400 bed general private hospital where pharmacists join the doctor-nurse team by working in a dispensing unit location on each 100 bed nursing unit or in the central pharmacy. The dispensing unit personnel have responsibility for providing drugs, oxygen, dressing trays, I.V. solutions and similar items. A total of sixteen staff pharmacists is required to staff the hospital. Applicants must be eligible for registration in California. Excellent opportunity; generous benefits. PO-148

STAFF OR ASST. CHIEF PHARMACIST—150 bed general hospital located in New Mexico. Generous benefits. PO-134

STAFF PHARMACIST—500 bed general hospital located in Oklahoma. B. S. required. Forty hour week. PO-95

ASST. CHIEF PHARMACIST—237 bed general hospital in West Virginia. Female desired. Forty-four hour week, vacation. PO-77

positions wanted

CHIEF PHARMACIST—Male, married. Eight years' hospital pharmacy experience. Will locate anywhere. Registered in New York, Pennsylvania and Florida. PW-288

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. obtained at University of Illinois. Extensive hospital pharmacy experience. Prefers to locate in the East or Midwest. Registered in Illinois. PW-287

STAFF OR ASST. CHIEF PHARMACIST—Male, married. Obtained B. S. in 1954 at Rutgers College of Pharmacy. Hospital pharmacy experience. Prefers to locate in Florida. Registered in Florida, New Jersey and New York. PW-286

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. received at Purdue University in 1944. Served hospital pharmacy internship. Extensive hospital pharmacy experience. Will locate anywhere. Registered in Indiana, Michigan and Wisconsin. PW-285

STAFF OR ASST. CHIEF PHARMACIST—Male, single. Obtained B. S. in 1959 at the University of Colorado. Completed hospital pharmacy internship at Denver General Hospital in June 1960. Prefers to locate in the West or Midwest. Registered in Colorado. PW-284

ASST. CHIEF OR CHIEF PHARMACIST—Female. Obtained B. S. in 1955 at Xavier University. Five years' hospital pharmacy experience. Prefers to locate in the Los Angeles, California area. Registered in Louisiana and Texas. PW-283

ASST. CHIEF OR CHIEF PHARMACIST—Female, married. B. S. obtained in 1954. Six years' hospital pharmacy experience. Prefers to locate in New York, New Mexico and Texas. Registered in New York, New Mexico, Texas and Louisiana. PW-282

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Ph.G. Degree obtained at Philadelphia College of Pharmacy and Science. Extensive hospital pharmacy experience. Prefers to locate in the North or West. Registered in Pennsylvania, Wisconsin, and Michigan. PW-281

SAFF OR ASST. CHIEF PHARMACIST—Male, married. M. S. Degree obtained in 1958 at the State University of Iowa. Two years' hospital pharmacy experience. Served hospital pharmacy internship. Prefers to locate in California. Registered in New York. PW-280

CHIEF PHARMACIST—Male, married. Obtained B. S. in 1953 at St. John's College of Pharmacy. Seven years' hospital pharmacy experience. Prefers to locate in the Northeast. Registered in New York and New Jersey. PW-279

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. M. S. Degree obtained in September 1960 at Oregon State College. Hospital pharmacy experience. Served hospital pharmacy internship. Interested in a position with teaching duties. Prefers to locate in Ohio, Pennsylvania, or Indiana. Registered in Oregon but will reciprocate. PW-278

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Received at Ohio State University B. S. Degree in Biology in 1952 and B. S. Degree in Pharmacy in 1955. Five years' hospital pharmacy experience. Willing to locate in the Eastern, Northern or Western part of the country. Registered in Ohio. PW-277

ASST. CHIEF OR CHIEF PHARMACIST—Female, single. B. S. obtained in 1956 at the University of Wyoming. Completion of work for M. S. Degree expected fall of 1960 at the University of Maryland. Served hospital pharmacy internship. Hospital pharmacy experience. Prefers to locate in the West. Registered in Wyoming. PW-276

STAFF OR ASST. CHIEF PHARMACIST—Female, married. B. S. obtained in 1954 at St. Louis College of Pharmacy. Six years' hospital pharmacy experience. Prefers the Northwestern part of the country, but willing to locate anywhere. Registered in Missouri. PW-275

CHIEF PHARMACIST—Male, married. Obtained M. S. in Hospital Pharmacy in 1954 at the University of Southern California. Served hospital pharmacy internship. Eight years' hospital pharmacy experience. Prefers to locate in the Northeastern part of the country. Registered in New York, New Jersey and California. PW-274

ASST. CHIEF OR CHIEF PHARMACIST—Male, single. Obtained M. S. in 1959 at the Medical College of Virginia. Served hospital pharmacy internship. Military obligation completed. Will be available for employment during September. Prefers to locate in the East. Registered in New Jersey. PW-273

CHIEF PHARMACIST—Male, married. Received B. S. Degree in 1957 at Purdue University. Two years' hospital pharmacy experience. Tour of duty in U. S. Army will be completed in September. Prefers to locate in the Southeastern part of country. Registered in Indiana and Illinois. PW-272

STAFF PHARMACIST—Male, married. Obtained B. S. in 1952 at Duquesne University. Prefers to locate in the Pittsburgh area. Registered in Pennsylvania. PW-271

ASST. CHIEF OR CHIEF PHARMACIST—Male, single. M. S. obtained in 1958 at the University of Texas. Served hospital pharmacy internship. Hospital pharmacy experience. Prefers to locate in the Southwest. Registered in Kansas and Texas. PW-270

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. obtained in 1955 at the University of Nebraska. Hospital pharmacy experience. Prefers to locate in the West or Midwest. Registered in Nebraska. PW-269

CHIEF PHARMACIST—Male, single. Obtained M. S. in 1954 at the University of Tennessee. Served hospital pharmacy internship. Six years' hospital pharmacy experience. Prefers to locate in the southwest or in Florida. Registered in Connecticut and New York. PW-266

CHIEF PHARMACIST—Male, married. M. S. obtained in 1957 at the Nebraska University College of Pharmacy. Served hospital pharmacy internship. Six years' hospital pharmacy experience. Prefers to locate in the West or Midwest. Registered in Colorado, Missouri and Nebraska. PW-265

CHIEF PHARMACIST—Male, married. Obtained M. S. in Hospital Pharmacy at the State University of Iowa in June 1959. Served hospital pharmacy internship. Three years' hospital pharmacy experience. Will locate anywhere. Registered in Illinois. PW-264

CHIEF PHARMACIST—Male, married. B. S. Served hospital pharmacy internship. Extensive hospital pharmacy experience. Prefers to locate in the Midwest. Registered in Ohio. PW-263

ASST. CHIEF PHARMACIST—Male, single. Obtained B. S. in 1956 at Purdue University. Hospital pharmacy experience. Prefers position with some administrative and/or teaching duties. Would like to locate in Northeast or Southwest section of country. Registered in Texas. PW-256

CHIEF PHARMACIST—Male, single. B. S. obtained in 1952 at the University of Illinois. Served hospital pharmacy internship. Two years' hospital pharmacy experience. Registered in Illinois. Prefers to locate in Arizona. PW-252

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Obtained B. S. in 1954 at South Dakota State College. Two years' hospital pharmacy experience. Will locate anywhere. Registered in South Dakota. PW-247

STAFF PHARMACIST—Male, married. Received B. S. in June 1960 at Philadelphia College of Pharmacy and Science. One year's hospital pharmacy experience. Prefers to locate in Philadelphia. PW-246

DIRECTOR OF PHARMACY SERVICES—Male, single. Received B. S. in 1956 at the University of California. Served hospital pharmacy internship. Four years' hospital pharmacy experience. Registered in California. Prefers to locate in California. PW-237

PHARMACIST—Female, single. M. S. received at the University of Maryland in 1951. Served hospital pharmacy internship. Five years' hospital pharmacy experience. Prefers to locate in New Jersey. Registered in Pennsylvania and Missouri. PW-225

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. received at Detroit Institute of Technology in 1950. Four years' hospital pharmacy experience. Prefers to locate in Michigan. Registered in Michigan. PW-224

CHIEF PHARMACIST—Male, single. B. S. received in 1952 at Massachusetts College of Pharmacy. Seven years' hospital pharmacy experience. Will locate anywhere. Registered in Massachusetts. PW-218

STAFF OR CHIEF PHARMACIST—Male, single. B. S. received in 1952 at St. Louis College of Pharmacy. Two years' hospital pharmacy experience. Registered in Missouri. Prefers to locate on the West Coast, particularly California. PW-217

STAFF PHARMACIST—Female, single. B. S. Seven years' hospital pharmacy experience. Southwest section of country preferred. Registered in Alabama and Georgia. PW-199

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. M. S. obtained in 1956 at Columbia University College of Pharmacy. Hospital experience. Prefers to locate in California. Registered in New York, Michigan, New Jersey and Florida. PW-184

ASST. CHIEF OR CHIEF PHARMACIST—Male. B. S. received in 1954. Desires to locate in Michigan, Ohio or Illinois. Registered in Michigan. PW-177

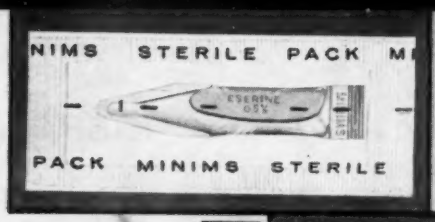
CHIEF PHARMACIST—Male, married. B. S. Ten years' hospital pharmacy experience. Registered in Mass., Ill., Mo., Ky., Tenn., and Va. PW-150

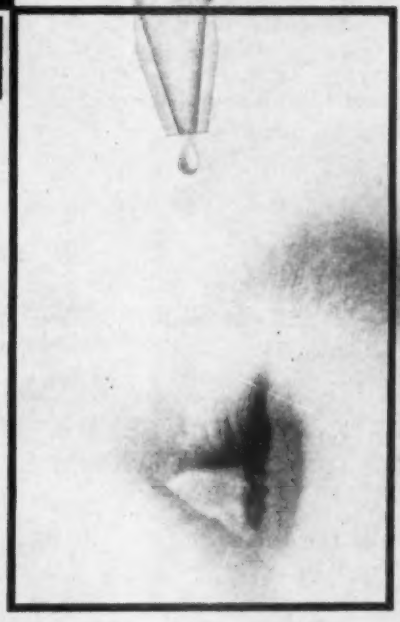
ASST. CHIEF OR CHIEF PHARMACIST—Male, single. Registered in D. C., Ill., Md., and Pa. Graduate University of Pittsburgh in 1953, experience in research. Prefers North and East. PW-148

CHIEF PHARMACIST—Male, married. Graduate of St. John's University College of Pharmacy. Extensive experience as chief pharmacist and purchasing agent. Prefers to locate in New York or New Jersey. Registered in New York and New Jersey. PW-144

ASST. DIRECTOR OR DIRECTOR OF PHARMACY SERVICES—Male, single. B. S. Retail and five years' hospital experience. Registered in Illinois. PW-119

CHIEF PHARMACIST—Female, single. Registered in Pennsylvania and Ohio. Twelve years' hospital pharmacy experience as a chief pharmacist. Desires to locate in Pennsylvania or Ohio. PW-111





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